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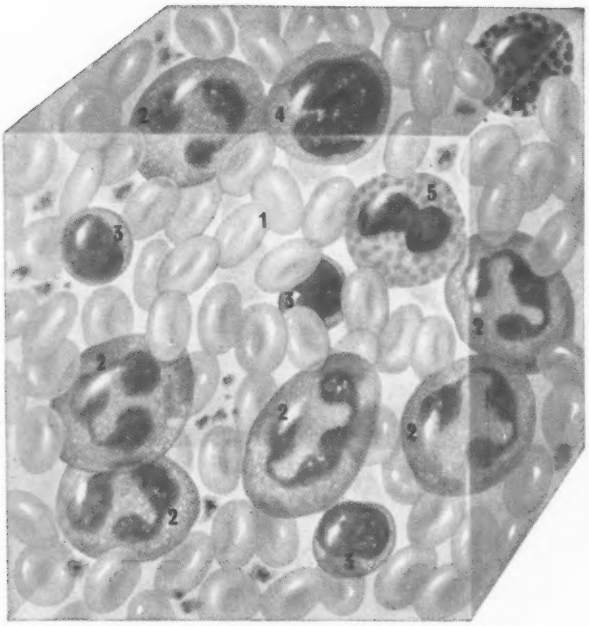
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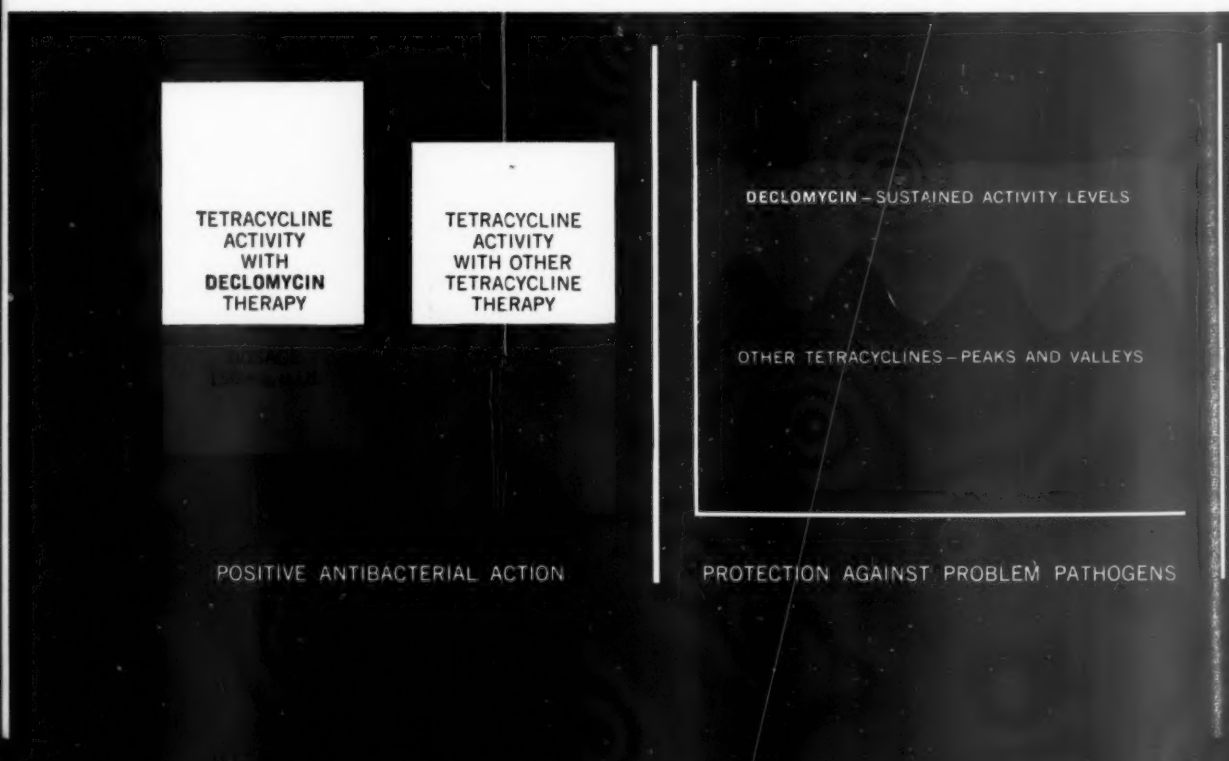
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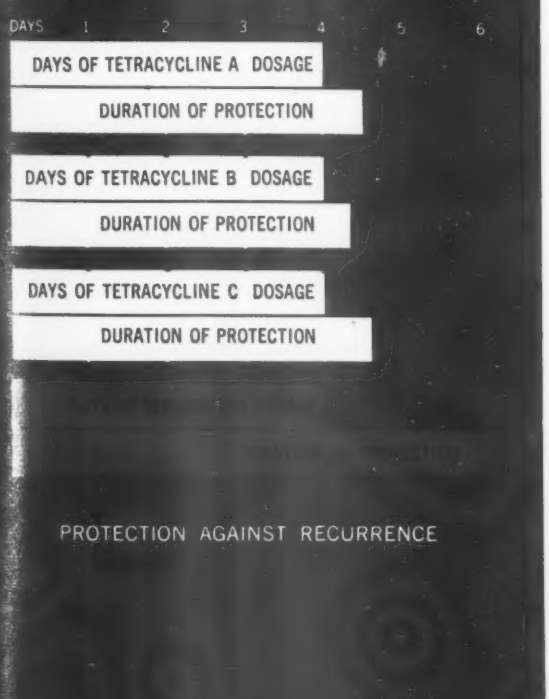


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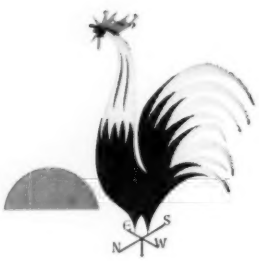
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And, Gentia-jel is easy for your patients to use. (1) Prior to retiring for the night, patients lie back with knees flexed, insert applicator and instill Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators.

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brand of bisacodyl tablets and suppositories

the laxative with a bibliography

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The extensive bibliography* on Dulcolax, amounting to almost 100 clinical reports, strongly affirms its clinical advantages.

Induces Natural Evacuation
The action of Dulcolax is based on simple reflex production of large bowel peristalsis on contact with the colonic mucosa. As a result, stools are usually soft and well formed and purgation is avoided.

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With Dulcolax tablets action is almost invariably obtained overnight... with suppositories action occurs within the hour.

Wide Application
Dulcolax is as well adapted to preparation for radiographic and operative procedures as it is to the treatment of constipation.

*Detailed literature, including complete bibliography, available on request.

Dulcolax®, brand of bisacodyl: Tablets of 5 mg. and suppositories of 10 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

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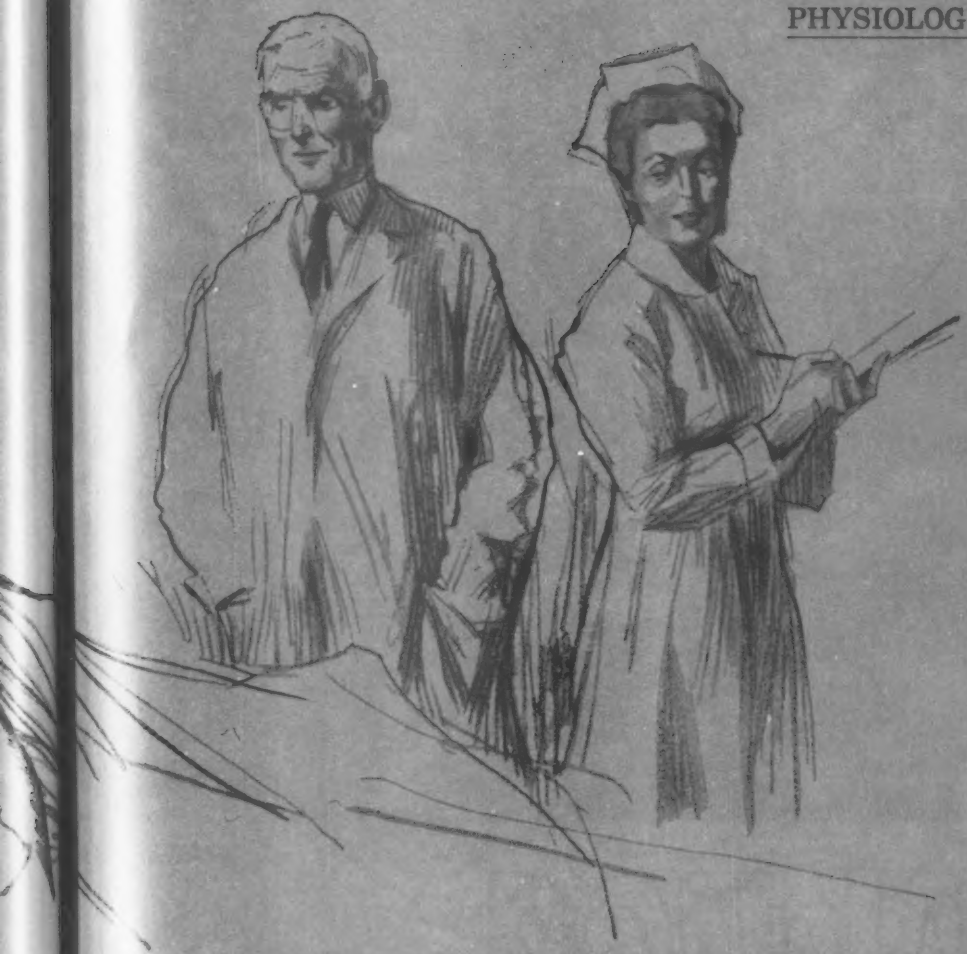
· *relief for the patient*

– prophylactic use of 'Urecholine' soon after surgery or childbirth often prevents painful urinary retention; therapeutically, 'Urecholine' rapidly facilitates micturition, without subjecting the patient to the discomfort of catheterization.

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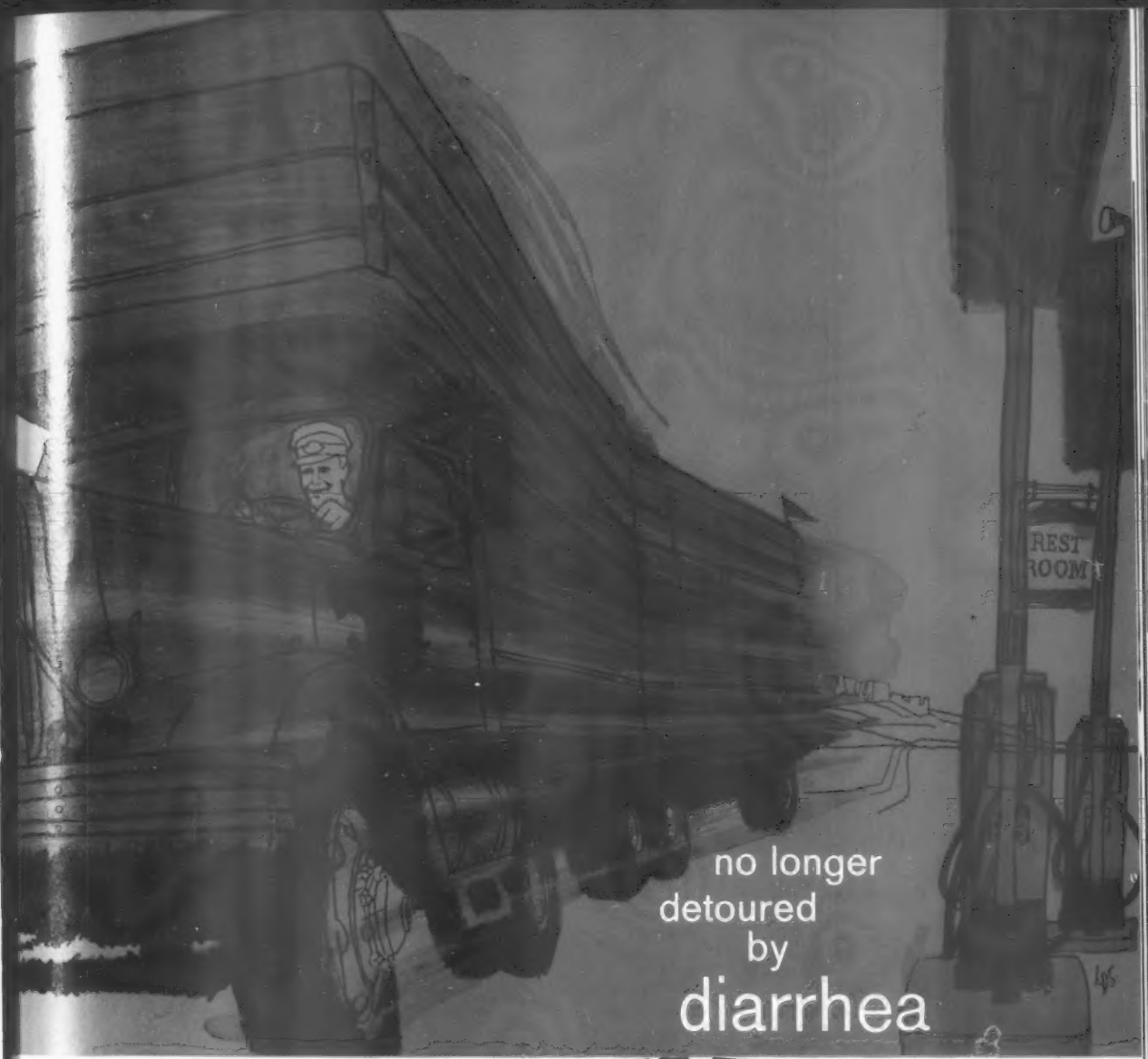
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		hyoscine hydrobromide	0.0065 mg.

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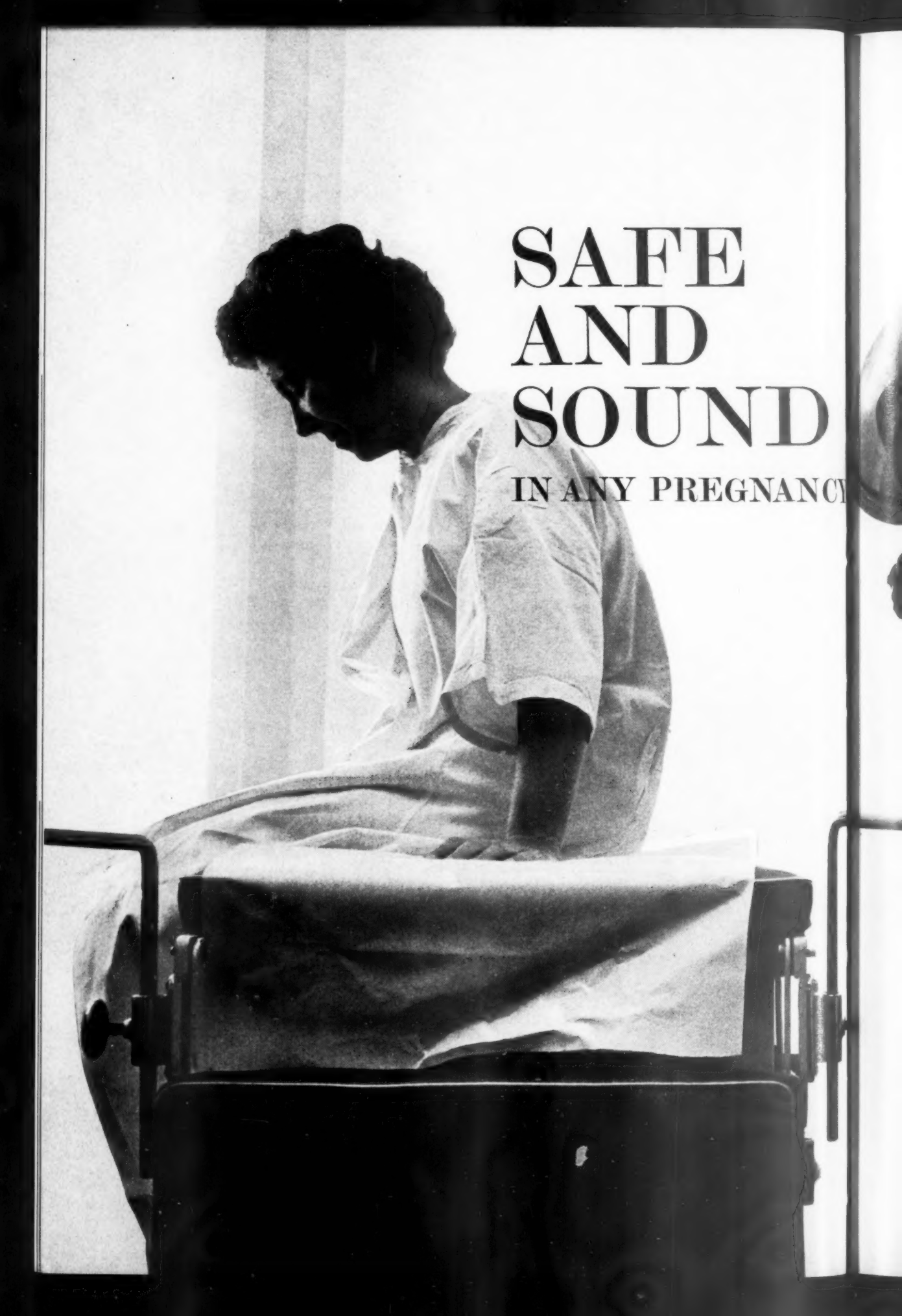
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References: 1. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 2. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.

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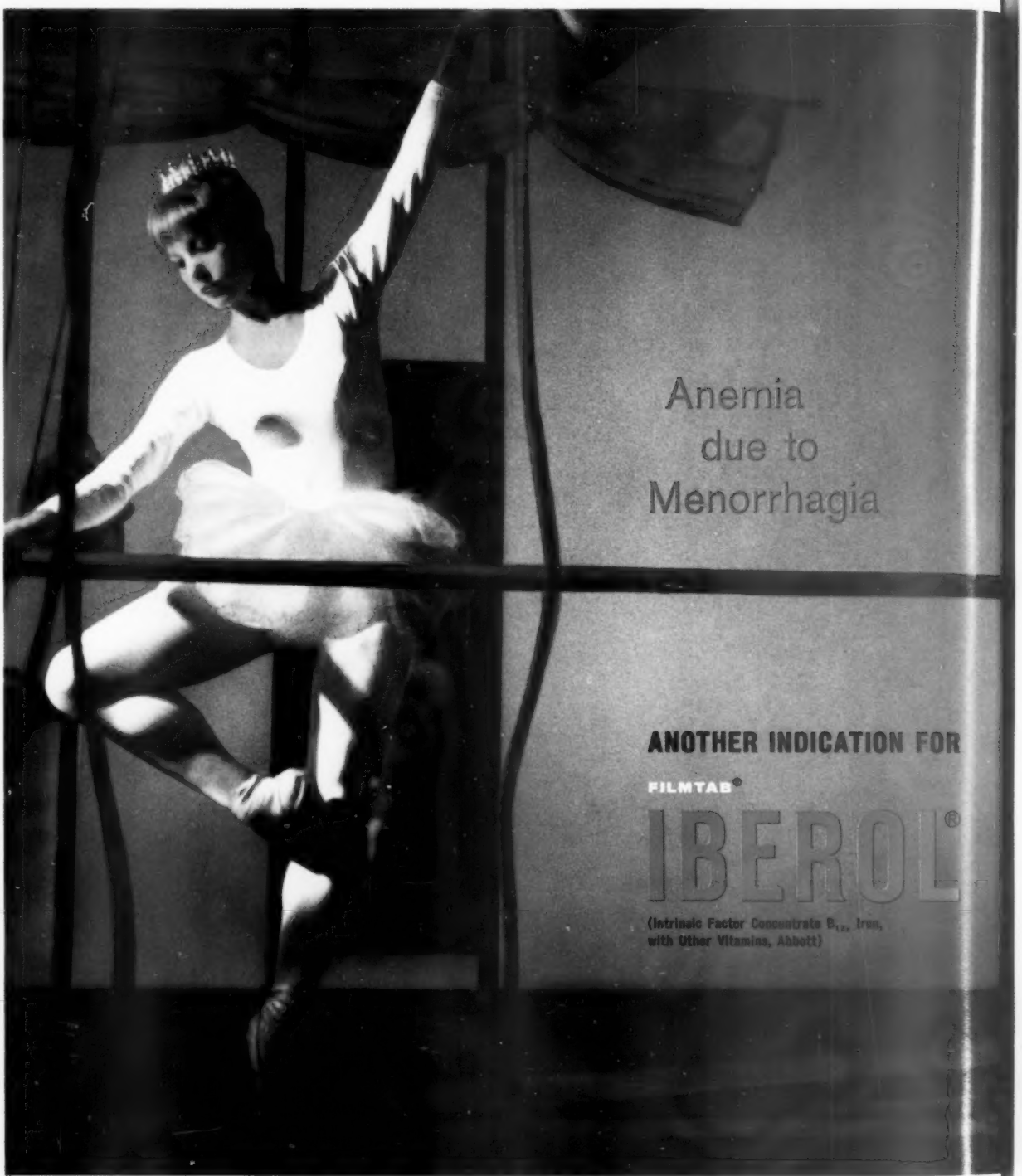
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The *buffered* acid douche solution of Massengill Powder (pH 3.5-4.5) resists neutralizing. And this normal, low pH is maintained for 4 to 6 hours in ambulant patients . . . and as long as 24 hours in recumbent patients.

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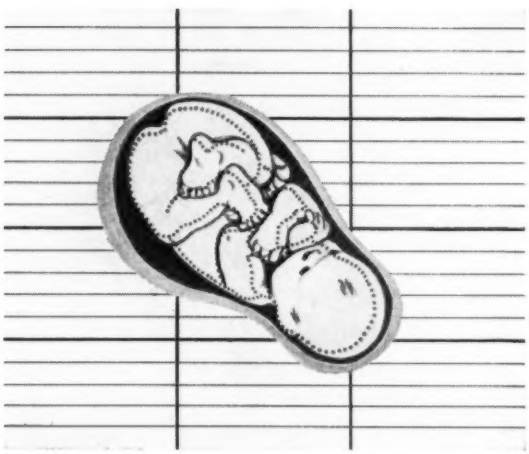
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Anthraquinone derivatives from cascara and dioctyl sodium sulfosuccinate, Mead Johnson

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Peri-Colace, a unique combination of Peristim® and Colace® (dioctyl sodium sulfosuccinate) "...gave satisfactory results in 97 per cent of the cases [130 hospitalized patients]."[2]

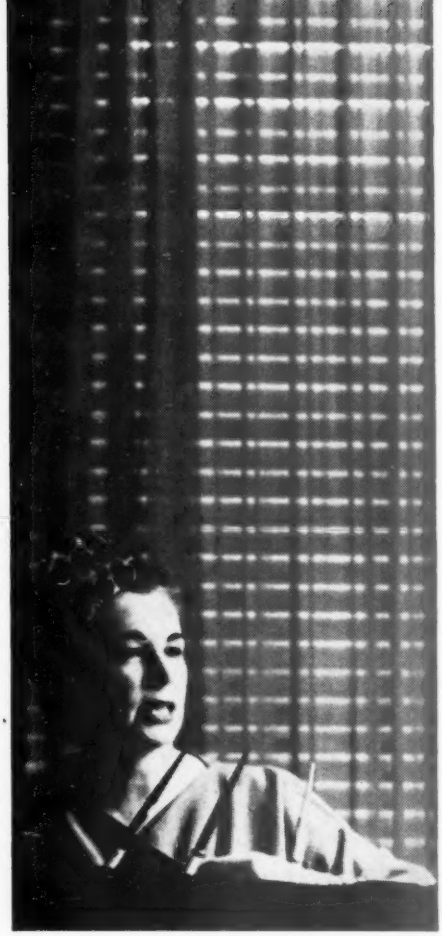
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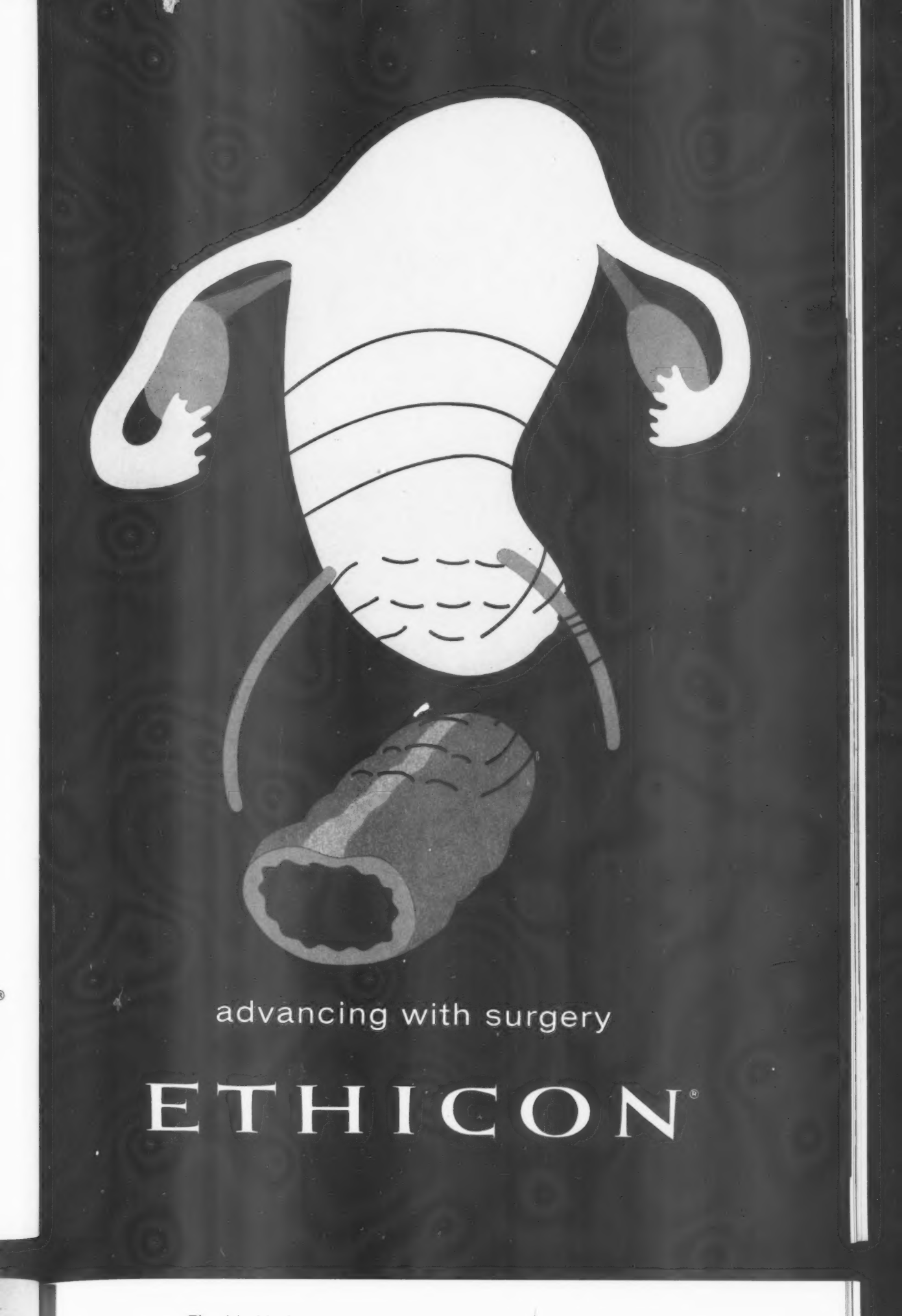
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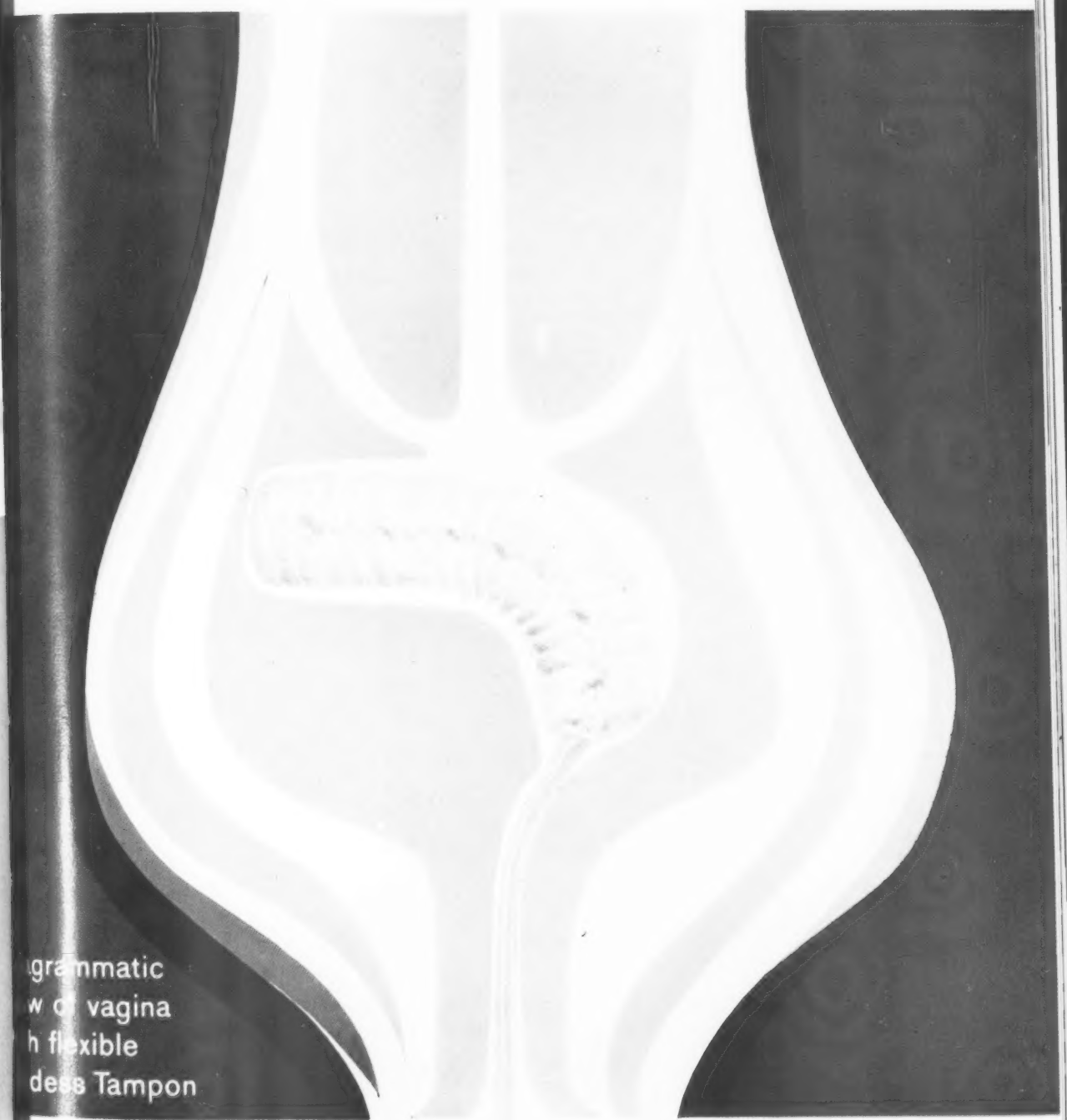
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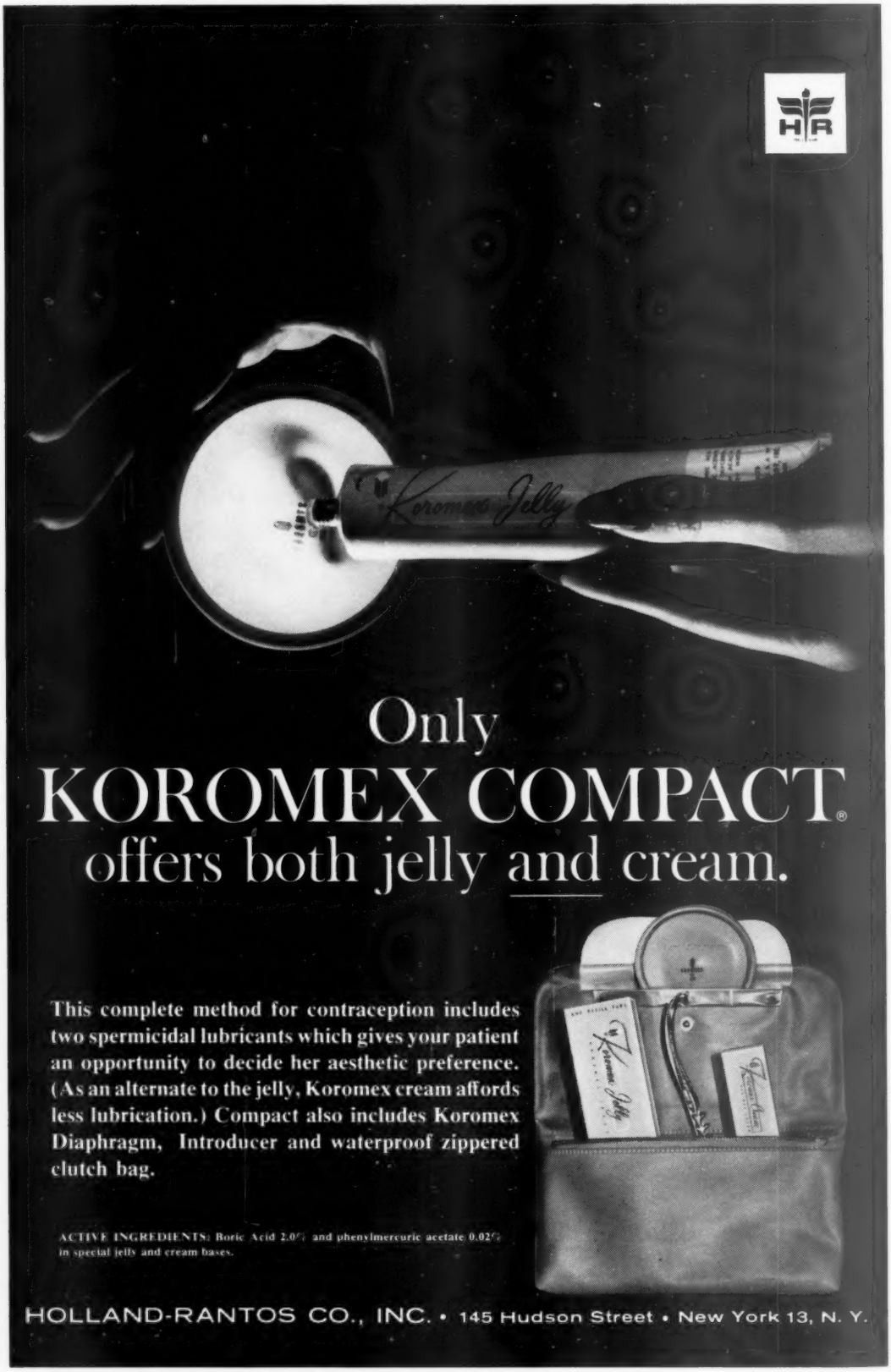
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Wissenschaftlicher Assistent der Universitäts-Frauenklinik Kiel.

In German language. With 85 illus. XIV, 634 pages Royal 8vo. 1961.

Cloth DM 148,—

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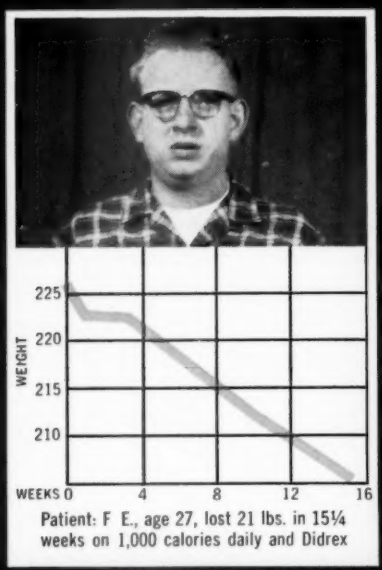
This textbook will summarize for the first time the overwhelming knowledge accumulated in the field of estrogens for the use of the laboratory worker, the clinician, but also the general practitioner. In addition to a great amount of methodological details, including a fair amount of unpublished data, this textbook will completely cover the chemistry, biochemistry, and physiology of estrogens in the human being. Normal values in blood, urine, and other body fluids and tissues are presented and the available information on estrogen values in pathological conditions systematically compiled and critically evaluated.

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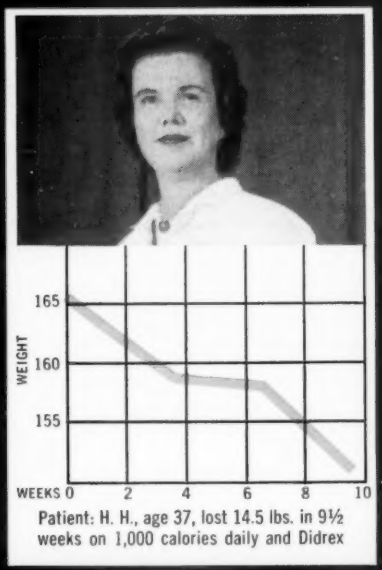
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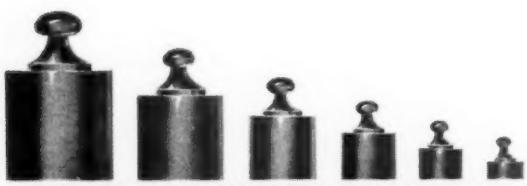


Patient: H. H., age 37, lost 14.5 lbs. in 9½ weeks on 1,000 calories daily and Didrex



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Put it to your patient this way: The basic therapeutic objective of obesity management is to change dietary habits built over months or years of weight accumulation. This takes time and will. Consider Didrex, the new Upjohn appetite suppressant. Happily, it elevates mood which makes dieting more acceptable. More important, it works: "persistent significant weight loss" in patients followed for as long as 20 weeks. Added to your favorite reducing regimen, ½ to 1 Didrex tablet one to three times daily is usually adequate to preclude the "weight plateau" that so often discourages dieters after a few weeks. Available as 50 mg. tablets in bottles of 100. **Upjohn**

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References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex®). Journal of the Oklahoma State Medical Association, 53:760-767 (November) 1960. 2. Oster, H., and Medlar, R.: A clinical pharmacologic study of benzphetamine (Didrex®), a new appetite suppressant. Arizona Medicine, 17:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex®). Current Therapeutic Research, 2:33-38 (February) 1960.

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Description: Didrex is the Upjohn brand of benzphetamine hydrochloride [(+)-N-benzyl-N,α-dimethyl-phenethylamine hydrochloride]. A sympathomimetic compound with marked anorectic action and relatively little stimulating effect on the CNS or cardiovascular system.

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Dosage: Initiate appetite control with ½ or 1 tablet (25 to 50 mg.) in midmorning for several days. Then adjust dosage to suit each patient's need to a maximum of 3 tablets daily (150 mg.).

Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

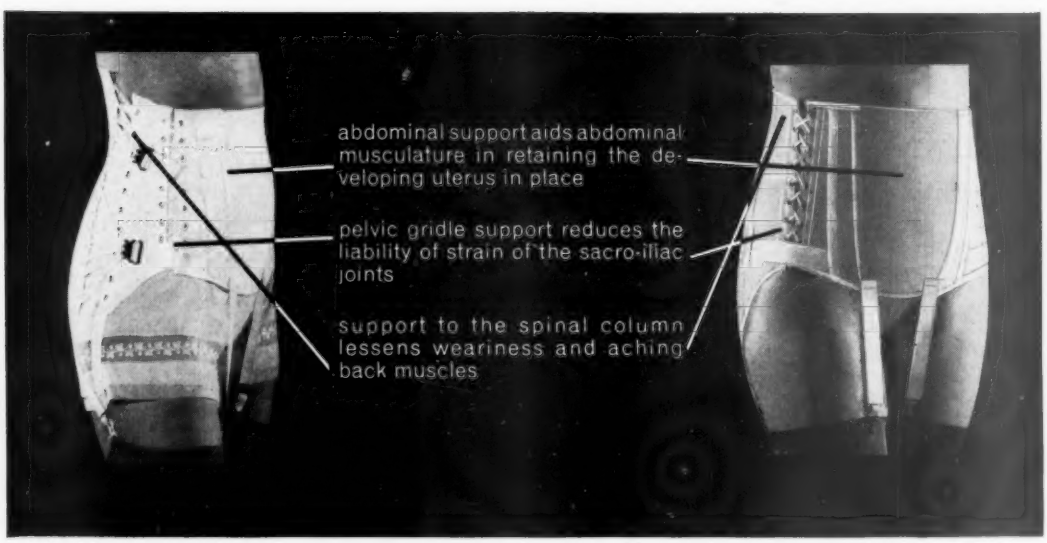
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definite support to loosened joints and pelvic girdle instability during pregnancy

Scientifically designed Camp prenatal supports offer the pregnant patient relief and protection in three specific areas: the abdominal wall, the pelvic girdle and the back. The reports of many obstetric authorities indicate prenatal supports help relieve tension on the abdominal walls and reduce discomfort from stretching muscles, cause a decrease in the appearance of striae gravidarum, improvement of muscular tone, and aid the return of venous blood from the extremities—thus diminishing the occurrence of varicose veins and edema. By functionally realigning the pelvis, support of the weight is transferred from the spine to the pelvis, posture is improved and better body balance created without undue constriction at any point. Camp manufactures lightweight non-supporting maternity girdles, garter belts and panty girdles as well as a complete selection of the sturdy support types illustrated above. There is a Camp garment available to accommodate any of your patient's prenatal requirements.



S. H. Camp and Company, Jackson, Michigan
S. H. Camp and Company of Canada, Ltd., Trenton, Ontario

CAMP
TRADE MARK

Antibiotic Moniliasis
Pregnancy Moniliasis
Diabetic Vulvitis
Persistent Mixed Infections

HYVA®
GENTIAN VIOLET
VAGINAL TABLETS

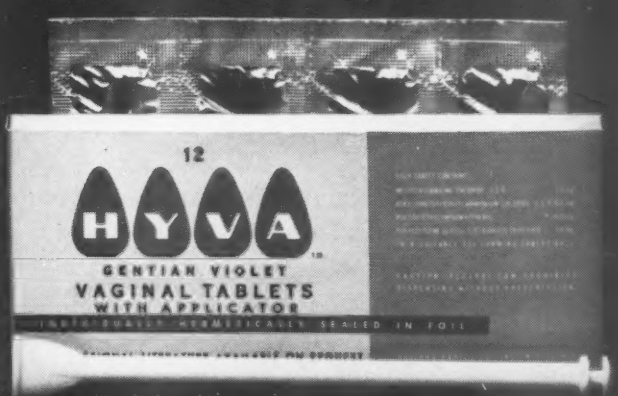
The only specific antimycotic vaginal tablet with a "gel" forming base. May be handled without staining.

- Simple to use · No messiness
- Shorter treatment time
- Aesthetically acceptable
- Potent fungicide and bactericide

Literature and sample available.

Supplied in boxes of 12 tablets, each hermetically sealed; convenient applicator.

ACTIVE INGREDIENTS: Alkyldimethylbenzylammonium chloride .05 mgm., Polyoxyethylenenonylphenol 10.0 mgm., Polyethlene Glycol Tert-Dodecylthioether 5.0 mgm.



HOLLAND-RANTOS CO., INC. • 145 Hudson Street • New York 13, N. Y.

IRON

PLUS THE BENEFITS OF A FECAL SOFTENER

NEW

FERRO

OPTIMAL RELEASE IN THE AREA OF OPTIMAL UPTAKE

FERRO-SEQUELS...a rational, physiologic approach to the treatment of iron deficiency...with an improved, better-tolerated medicinal iron...with sustained action timed for optimal release...plus the fecal softener dioctyl sodium sulfosuccinate.

The better-tolerated ferrous fumarate is made available in optimal amounts at the sites where uptake is most efficiently accomplished. The bulk of the iron is timed for release through the duodenum-jejunum, and virtually all of the remainder in the ileum—thus corresponding closely to the normal sequence of absorption of medicinal iron described by Goodman and Gilman.[2]

The possibility of gastrointestinal irritation is greatly reduced...first, because of the excellent toleration of ferrous fumarate[1, 3-6]...second, because the concentration of iron salt is not unduly high at any one point.

Dioctyl sodium sulfosuccinate helps soften stools for easier elimination.

Each two-tone, green FERRO-SEQUELS capsule contains:

Ferrous fumarate (equivalent to 50 mg. elemental iron)	150 mg.
Dioctyl sodium sulfosuccinate	100 mg.

Bottle of 30.

Dosage: 1 or 2 SEQUELS® daily.

Bibliography—1. Feldman, H. S.: Ferrous Fumarate in the Treatment of Iron Deficiency Anemia. Virginia M. Month. 87:177 (April) 1960. **2.** Goodman, L. S., and Gilman, A.: Pharmacological Basis of Therapeutics, Second Edition, Macmillan, New York, 1955, p. 1455. **3.** Illingworth, D. G.: Ferrous Fumarate. Brit. M. J. II (5159):1099 (Nov. 21) 1959. **4.** New and Nonofficial Drugs: Ferrous Fumarate. J.A.M.A. 171:1104 (Oct. 24) 1959. **5.** Shapleigh, J. B., and Montgomery, A.: Ferrous Fumarate: A Clinical Trial of a New Iron Compound. Am. Pract. 10 (3):461 (Mar.) 1959. **6.** Swan, H. T., and Jowett, G. H.: Treatment of Iron Deficiency with Ferrous Fumarate. Assessment by a Statistically Accurate Method. Brit. M. J. II (5155):782 (Oct. 24) 1959.

SEQUELS®

SUSTAINED RELEASE IRON CAPSULES LEDERLE

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

only 2 seconds to specify MAXIMUM QUALITY

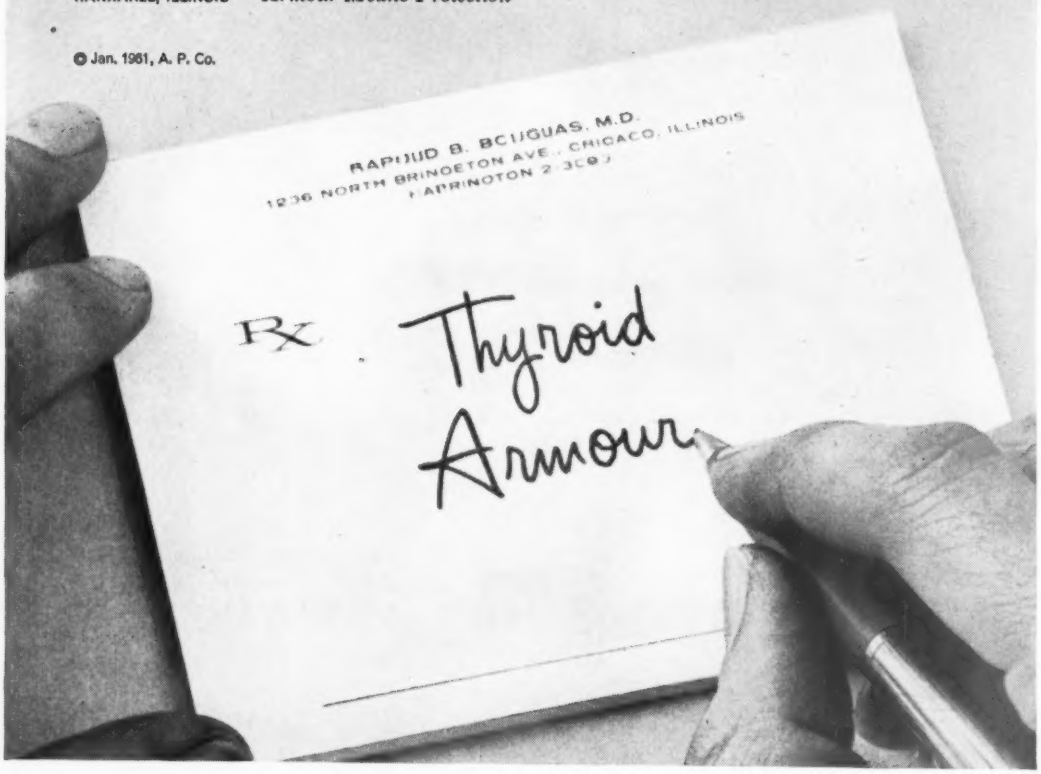
It takes only 2 seconds to specify "THYROID ARMOUR" on a prescription blank, yet these words represent the highest grade thyroid available, manufactured with all the control skills learned during three-quarters of a century of experience with endocrine products. THYROID ARMOUR is the original standard of comparison for all thyroid preparations, and is regarded throughout the world as the quality thyroid product.

THYROID U.S.P.

Thyroid Tablets (Armour) are prepared from fresh selected glands, desiccated and standardized by official U.S.P. method to contain 0.2 per cent of iodine in thyroid combination. Thyroid Powder U.S.P. (Armour) is standardized and of uniform potency. USES: Thyroid deficiencies, cretinism, myxedema, nodular goiter (non-toxic), non-nodular goiter. A variety of clinical conditions will respond to the use of Thyroid (Armour) when subclinical hypothyroidism is involved, i.e., gynecologic conditions such as functional menstrual disorders, sterility, habitual abortion; recurring conjunctivitis; certain types of anemias and obesity; and certain changes which occur in hair, skin and fingernails. DOSAGE: ¼ to 5 grains daily as required by clinical condition. Therapeutic effect develops slowly and lasts for two months or longer. Thus the daily dose may be given as a single dose (preferably in the morning) rather than several times daily. Patients treated with thyroid should be continuously under the physician's observation. CONTRAINDICATIONS: Heart disease and hypertension, unless the metabolic rate is low. SUPPLIED: Tablets—bottles of 100, 1000 and larger: potencies of ¼, ½, 1, 2 and 5 grains. Powder—1 oz. 4 oz., and 1 lb. bottles.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS *Armour Means Protection*

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Thanks to your prompt treatment and the smooth action of Deprol, your patient's depression is relieved and her anxiety calmed—*often in two or three days.* She eats properly, sleeps well, and her depression no longer complicates your basic regimen.

Lifts depression...as it calms anxiety!

For pregnant, postpartum and menopausal patients—a smooth, balanced action that lifts depression as it calms anxiety...rapidly and safely

Balances the mood—no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient—*they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation—*they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety.

Acts swiftly—the patient often feels better, sleeps better, within two or three days. Unlike most other antidepressant drugs, Deprol relieves the patient quickly—often within two or three days.

Acts safely—no psychotic reactions. Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic therapy.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

▲Deprol▲®

WALLACE LABORATORIES
Cranbury, N. J.

CO-759



how shall she dress ? she wants to know now ..... you can tell her

(even in the first week)

with



Pro-Duosterone®

anhydrohydroxyprogesterone, 50 mg.
ethinyl estradiol, 0.03 mg. } per tablet

the 3-day, oral test for early diagnosis of pregnancy

If she is not pregnant, and has previously had regular menstrual cycles, withdrawal bleeding will occur within a few days after PRO-DUOSTERONE (1 tablet q.i.d. for 3 days). In functional amenorrhea, regular cycles are often restored.

If she is pregnant, no progesterone withdrawal bleeding can occur. PRO-DUOSTERONE actually protects pregnancy, and may be indicated to help improve implantation in habitual abortion.

". . . *a safe, physiologic method* . . . "[1], the convenient PRO-DUOSTERONE test has proved highly accurate (95.2% in 1,553 clinical studies) as early as a week after the first missed menses when animal tests cannot be considered valid.

Supplied: Bottles of 24 tablets.

1. Hayden, G.E.: Am. J. Obst. & Gynec. *76*:271, 1958.

ROUSSEL — **Roussel Corporation,** 155 East 44th Street, New York 17, N.Y.



happy mother, cheerful baby

because their physician has kept
her baby well nourished, healthy—and

free from diaper rash

with **DESITIN®**

OINTMENT

Protects against irritation of urine and excrement; markedly inhibits ammonia-producing bacteria; soothes, lubricates, stimulates healing.

For **samples** of Desitin Ointment, pioneer external cod liver oil therapy, write...

DESITIN CHEMICAL COMPANY
812 Branch Avenue, Providence 4, R.I.

Capillary protective measures in pregnancy

Prenatal treatment and threatened abortion

During pregnancy, fragile capillaries, increased capillary permeability, decidual bleeding, and the tendency toward edema are well recognized. Essential capillary protective factors are an integral part of the prenatal regimen.

The inclusion of Hesperidin or other citrus bioflavonoids as a "precautionary measure" in every pregnancy and as an "essential measure" in habitual aborters insures the restoration and maintenance of capillary integrity and helps prevent spontaneous abortion.

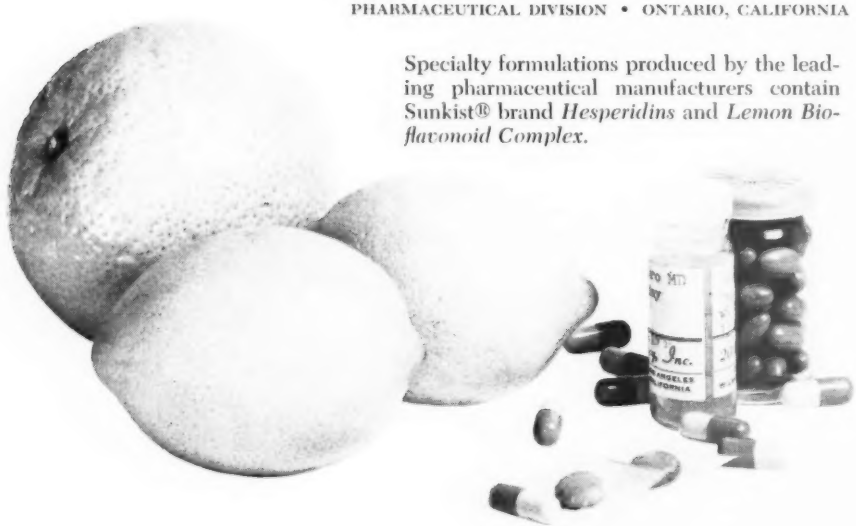
The rationale of Hespiridin and other citrus bioflavonoids – in conjunction with vitamin C, nutritional factors and other therapeutic measures – as adjuncts, is based on the premise that capillary involvement may be a contributing factor in spontaneous abortion and erythroblastosis fetalis.

Hesperidin, Lemon Bioflavonoid Complex and their naturally occurring synergist ascorbic acid are readily available capillary protective factors for the restoration and maintenance of capillary integrity and function.

Sunkist Growers

PHARMACEUTICAL DIVISION • ONTARIO, CALIFORNIA

Specialty formulations produced by the leading pharmaceutical manufacturers contain Sunkist® brand *Hesperidins* and *Lemon Bioflavonoid Complex.*



in postmenopausal vaginitis
in vaginal plastic surgery

ORTHO®

Dienestrol CREAM

vaginal estrogen therapy

builds vaginal epithelium





The Clinical Study: A "double blind" investigation to evaluate Desoxyn as an aid in controlling weight during pregnancy.

The Patients: 60 pregnant women divided into two groups. One group received Desoxyn each morning, while the other received a placebo of identical appearance.

The Dosage: 10 mg. of Desoxyn Gradumet, orally, *once daily,* in the morning.

The Clinical Result: The 30 patients taking Desoxyn gained an average of .302 pounds per week for an average of 15 weeks. Of these patients, *eight gained no weight at all.*

The women taking the placebo gained an average of .534 pounds per week for 16 weeks. Two did not gain.

The Record: During the study, nine of the Desoxyn patients were given diuretics, while 13 of the other women received the same treatment. One patient taking Desoxyn complained of nervousness, while two of the placebo group had the same reaction and reported nausea.

1. Bayly, M. A., Desoxyephedrine As An Aid In Weight Control For Pregnant Clinic Patients, Quart. Bull. Northwestern Univ. M. School, 34:93, 1960.

The Drug:

DESOXYN® Gradumet®

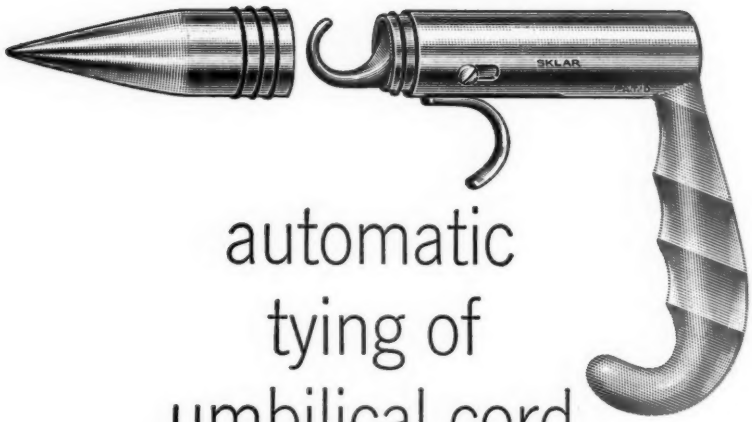
(Methamphetamine Hydrochloride in Long-Release Dose Form*)

All-day appetite control from a single oral dose—5, 10 or 15 mg.

*PAT. APPLIED FOR.

101185

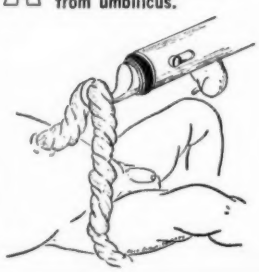
ABBOTT



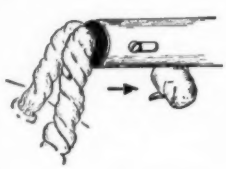
automatic tying of umbilical cord in 20 seconds with the GRAVLEE GUN*

by SKLAR

A Slack cord is looped over hook at desired distance from umbilicus.



B Trigger pull draws cord into barrel.

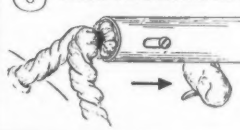


The Gravlee Gun provides a simple, positive, one-hand method for ligating umbilical cords of any size. Assures immediate and permanent hemostasis . . . prevents neonatal stump infections resulting from contaminated tapes or hands. Cords may be stripped if desired. The Gravlee Gun is sterilized by any of the conventional methods.[1]

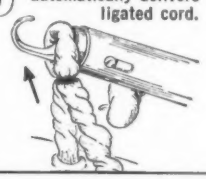
A SKLAR PRODUCT

Write for reprint and descriptive literature:
J. Sklar Manufacturing Co., Long Island City 4, N. Y.

C Additional pull slips sterile rubber band around cord.



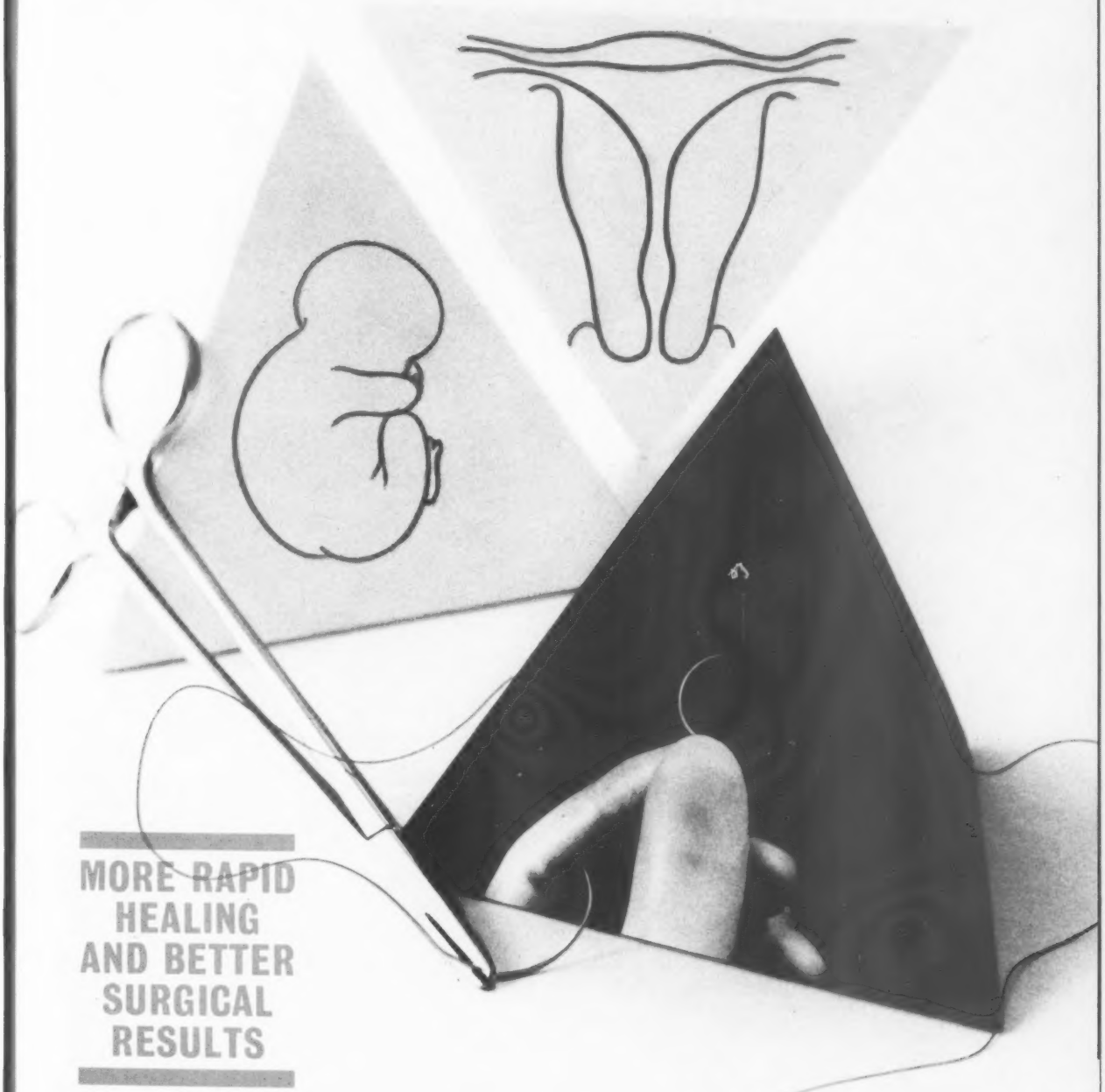
D Release of trigger automatically delivers ligated cord.



E Cord is clamped distally and cut in the usual manner.



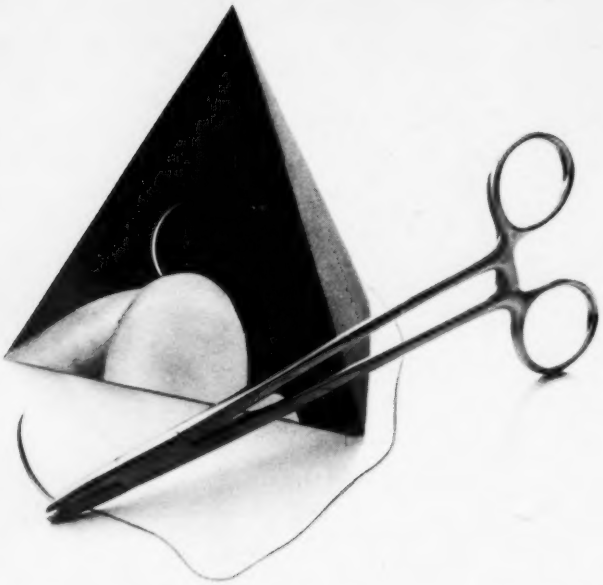
1. Gravlee, L. C., and Jones, W. N.: Obst. & Gynec. 15:43 (Jan.) 1960. * U. S. PAT. NO. 2,942,604.



MORE RAPID
HEALING
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SURGICAL
RESULTS

A PRODUCT OF THE SURGEON'S SKILL & TECHNIC
THE QUALITY LINE OF OB-GYN SUTURES

CYANAMID | SURGICAL PRODUCTS DIVISION



FOR OBSTETRIC AND GYNECOLOGIC PROCEDURES...

NEW HIGH TENSILE SURGICAL GUT

increased knot and tensile strength: Exclusive processing methods provide a completely uniform gut of higher knot strength plus improved tensile strength.

softer, smoother strand: Satin matte finish eliminates fraying. Gut is less irritating to tissue and holds knots more securely.

controlled absorption: Carefully controlled chromic processing maintains in situ gut strength during wound healing. Rigid laboratory digestion tests assure a uniform rate of absorption and compatibility with tissue.

armed on ATRAUMATIC® NEEDLES: New drilled end design permits uniform tempering of entire needle for greater strength. The needle holder may be placed far back on the needle shaft for greater tissue "bite". Flat surface opposite cutting edge is carried back on the needle shaft for a firm grip in the needle holder.

and to assist in episiotomy repair . . . DOUBLE-ARMED EPISIORRHAPHY SUTURE. Just cut strand to needed length to get two sutures: one with taper needle for deep tissue work; one with cutting needle for subcuticular stitching and, if desired, skin closure.

All sutures are available in the safer, easy-to-dispense SURGILOPE SP® Sterile Suture Strip Pack—winner of the 1960 Packaging Institute Award for the most outstanding advance in applied packaging technology.

CYANAMID | SURGICAL PRODUCTS DIVISION

AMERICAN CYANAMID COMPANY · 30 ROCKEFELLER PLAZA · N. Y., N. Y. · SALES OFFICE: DANBURY, CONN.



NEEDED: THE APPETITE SUPPRESSANT STRONG ENOUGH AND SAFE ENOUGH TO DO THE JOB

Ambar controls many cases of overeating/obesity refractory to usual therapy. To strengthen the will for successful dieting, the methamphetamine-phenobarbital in Ambar is designed to improve mood without harmful CNS overstimulation. Available in different forms to enable individualization of dosage: **AMBAR #1 EXTENTABS,** 10-12 hour extended action tablets, methamphetamine HCl 10.0 mg., phenobarbital 64.8 mg. **AMBAR #2 EXTENTABS,** methamphetamine HCl 15.0 mg., phenobarbital 64.8 mg. Also conventional **AMBAR TABLETS,** methamphetamine 3.33 mg., phenobarbital 21.6 mg.

A. H. ROBINS CO., INC., RICHMOND 20, VA.

Robins

Ambar™ #1 Extentabs® / Ambar™ #2 Extentabs®

The underlying causes of constipation are generally conceded to be atony of the bowel, biliary stasis, and the loss of excessive amounts of water from the stool.

Bile salts, the natural body laxative, increases the flow of hepatic bile, improving emulsification of fats and absorption of fat soluble vitamins.

A balanced combination of digestant, choleretic and stimulaxant ingredients can help to restore the normal pattern of elimination gently and physiologically.

The hydrotropic action insures the formation and passage of normal stools.

Stimulant laxatives effectively increase the muscular activity of the colon and promote return to regularity.

in other words..

Caroid and Bile Salts Tablets correct constipation physiologically by aiding protein digestion, increasing the flow of bile into the gut, and stimulating peristalsis. ℞ two tablets before retiring—One natural movement in the morning.

Caroid® & Bile Salts Tablets—digestant—choleretic—laxative.
American Ferment Division, Breon Laboratories Inc., New York 18, N.Y.



Stops the itch she dreads to scratch

IN PRURITUS VULVAE—whatever its cause—ES-A-CORT helps you control the intolerable itching and embarrassment within minutes. ES-A-CORT'S balanced combination of hydrocortisone, estrogen, and vitamin A . . . potentiated by DOME'S exclusive ACID MANTLE vehicle . . . relieves inflammation, itching and edema; facilitates healing, and restores the normal tonicity, vitality and protective acidity of mucosa and skin. CAUTION: contraindicated in patients with carcinoma of breast or genitalia.

ES-A-CORTT.M

CREME (pH 4.6) **LOTION**

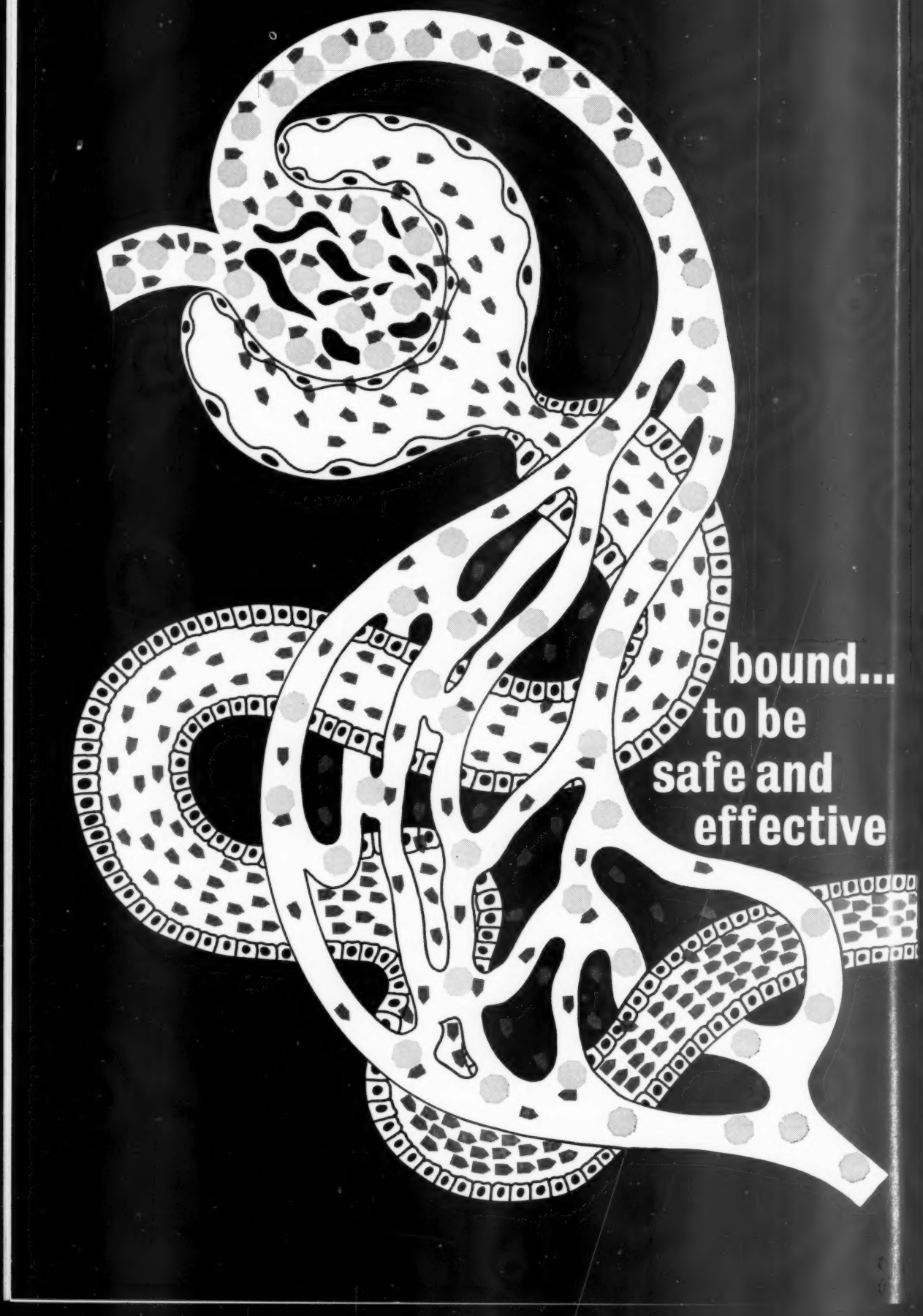
micronized hydrocortisone alcohol, vitamin A and estrone in the exclusive ACID MANTLE® vehicle.

DOME CHEMICALS INC.

New York Los Angeles

DOME

WORLD LEADER IN DERMATOLOGICALS


bound...
to be
safe and
effective

in any urinary tract infection: "it is the kidney which is the most important consideration"[1]... "Infections limited to the lower urinary tract are comparatively rare"[2]

In the bloodstream, free FURADANTIN and FURADANTIN bound to plasma proteins are in equilibrium ⇌ Free FURADANTIN passes readily through the glomerular filter. Protein-bound FURADANTIN, however, is not filtered by the glomerulus and reaches the peritubular capillaries. Here equilibrium is restored, and the FURADANTIN released from its bound state diffuses through the interstitial spaces and is secreted by the tubular cells. Exacting studies "suggest a three-component system for the renal transport of nitrofurantoin. That is, this nitrofuran appears to be filtered at the glomeruli and both secreted and reabsorbed by the tubules."[3]

Furadantin safeguards the kidney via a "three-component system of renal transport"[3]... insuring continuous, intimate contact with functioning renal tissue

For more than 8 years . . . in over 8,000,000* courses of treatment . . . a distinguished record of safety and efficacy

FURADANTIN®

brand of nitrofurantoin

"...may be given for extended periods of time without development of side effects or of drug-resistant mutants."[4]

"...was given continuously and safely for as long as three years."[5]

AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. tablet q.i.d. with meals and with food or milk on retiring.

SUPPLIED: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

*Conservative estimate based on clinical use since introduction.

REFERENCES: 1. Thompson, I. M.: Family Physician, Chicago 9:14, 1959. 2. Campbell, M. F.: Mod. Med. 24:85, 1956. 3. Paul, M. F., et al.: Am. J. Physiol. 197:580, 1959. 4. Johnson, S. H., III, and Marshall, M., Jr.: J. Urol., Balt. 82:162, 1959. 5. Lippman, R. W., et al.: J. Urol., Balt. 80:77, 1958.

® EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK



"be sure to make up more **TRICHOTINE** solution for our examining room."

You can see for yourself the efficient detergent action of Trichotine solution in reducing promptly a cervical plug (using a saturated cotton pledget), or washing away the "cheesy" exudate of monilia.

TRICHOTINE is just as effective for therapeutic irrigation by your patient at home

The same qualities – detergency*, antisepsis, healing – make Trichotine ideal for the treatment of cervico-vaginitis and leukorrheas, alone or in conjunction with other antimicrobials. In the itching, burning, and foul odor of non-specific vaginitis and leukorrhea the action of Trichotine is immediate and gratifying to the patient.

The more you expect of a douche, the more you will use Trichotine in the office and prescribe it for home irrigation, and recommend it as well for postmenstrual and postcoital hygiene.

The modern detergent douche

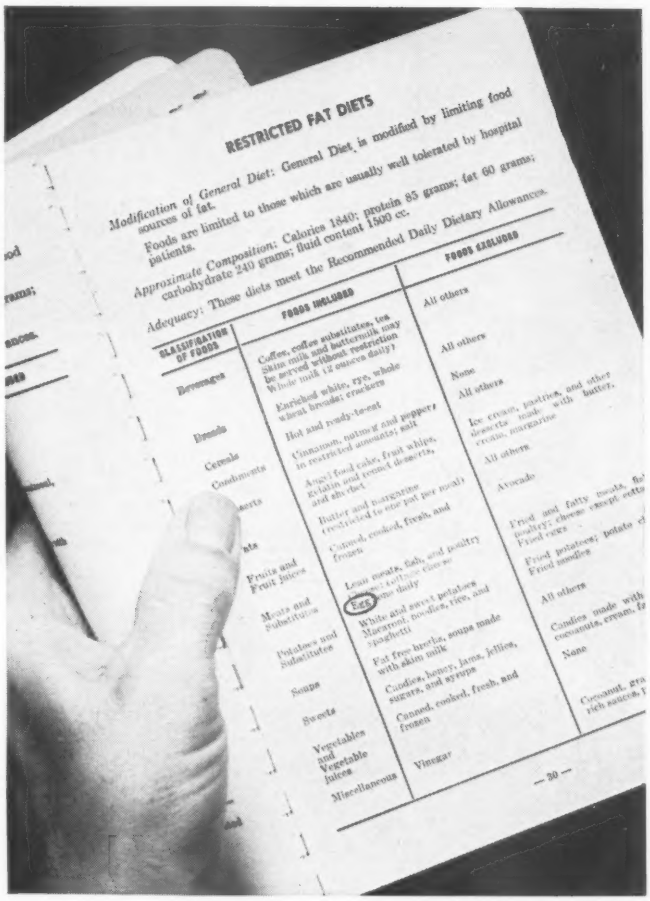
*SURFACE TENSION: TRICHOTINE 34 DYNES; VINEGAR 60 DYNES; TAP WATER 70 DYNES.

TRICHOTINE®

THE FESLER COMPANY, INC. 375 Fairfield Avenue, Stamford, Conn.

Medically Accepted

in so many restricted fat diets



RESTRICTED FAT DIETS

Modification of General Diet: General Diet is modified by limiting food sources of fat.

Foods are limited to those which are usually well tolerated by hospital patients.

Approximate Composition: Calories 1840; protein 85 grams; fat 60 grams; carbohydrate 240 grams; fluid content 1500 cc.

Adequacy: These diets meet the Recommended Daily Dietary Allowances.

CLASSIFICATION OF FOODS	FOODS INCLUDED	FOODS EXCLUDED
Beverages	Coffee, coffee substitutes, tea. Skim milk and buttermilk may be served without restriction. Whole milk 12 ounces daily.	All others
Breads	Enriched white, rye, whole wheat breads; crackers	All others
Cereals	Hot and ready-to-eat	None
Condiments	Cinnamon, nutmeg and peppery in restricted amounts; salt	All others
Desserts	Angel food cake, fruit whips, ices and ices; limited desserts.	Ice cream, pastries, and other desserts made with butter, cream, nonfat
	Butter and margarine restricted to one pat per meal)	All others
Fruits and Fruit Juices	Canned, cooked, fresh, and frozen	Avocado
Meats and Substitutes	Lean meats, fish, and poultry [illegible] daily	Fried and fatty meats, fish, poultry; cheese except cottage. Fried eggs
Potatoes and Substitutes	White and sweet potatoes. Macaroni, noodles, rice, and spaghetti	Fried potatoes; potato chips. Fried noodles
Soups	Fat free broths, soups made with skim milk	All others
Sweets	Candies, honey, jams, jellies, sugars, and syrups	Candies made with cocoanuts, cream, fat
Vegetables and Vegetable Juices	Canned, cooked, fresh, and frozen	None
Miscellaneous	Vinegar	Coconut, gravies, rich sauces, fat

— 30 —

The page here reproduced appears in the Diet Manual of the hospitals associated with Northwestern University Medical School, a distinguished teaching center.

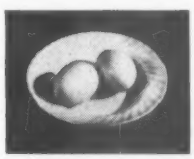


In diet manuals of medical teaching centers throughout the United States eggs are included in restricted fat diets.

This suggestion is based on the high overall nutritional value of eggs. The quality of egg protein is a standard against which other food protein is measured. The ratio of saturated to unsaturated fatty acids in egg yolk is in keeping with present-day thinking on this subject. The vitamin-mineral content supplies essentials for daily needs.

Eggs, one of the best sources of needed nutrients, fit into virtually every diet, including restricted fat, low sodium, low fiber, many other restricted diets, and of course the normal diet for all ages.

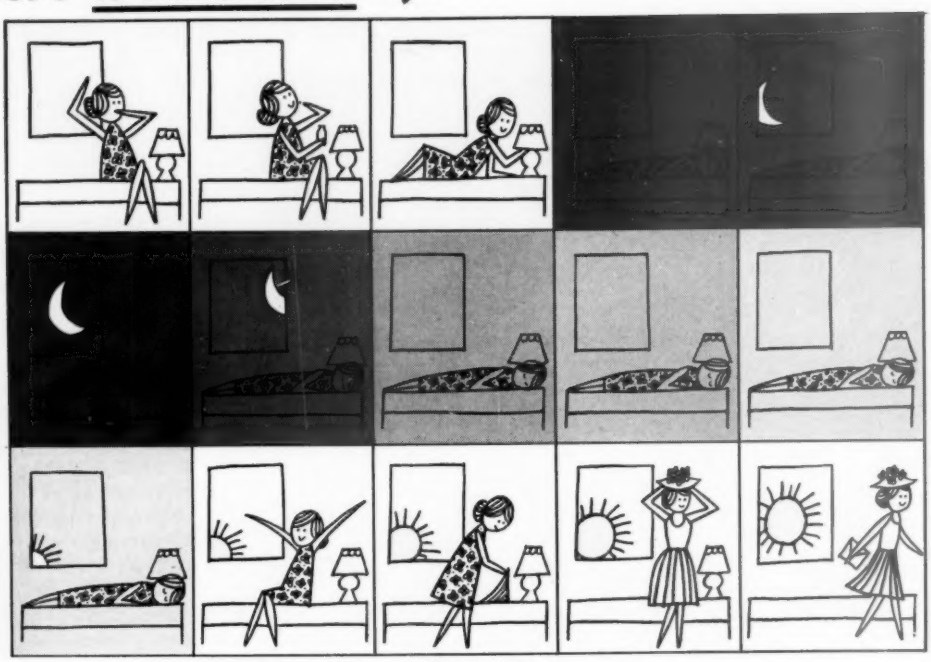
The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.



Poultry and Egg National Board
8 South Michigan Avenue, Chicago 3, Illinois

BENDECTIN

at bedtime



prevents
morning sickness
here!

"... I have gained the best results with [Bendectin]... Because these tablets have a protective coating... the dose taken at night becomes effective in the morning."[1]

NEW DOUBLE-BLIND STUDY SHOWS BENDECTIN EFFECTIVE IN 94% OF PATIENTS[2]

Medication	Number of patients	Complete relief	Partial relief	Failure
Bendectin	52	23 (44%)	26 (50%)	3 (6%)
		TOTAL 94%		
Placebo	57	13 (23%)	24 (42%)	20 (35%)
		TOTAL 65%		

"Bendectin was administered in a preliminary study to 146 patients and later, in a controlled, double-blind study to 52 patients, or to a total of 198 patients suffering from nausea and vomiting of pregnancy. A very gratifying therapeutic response was obtained in 178 or 90 per cent. In a double-blind portion of this study, the response of 52 patients treated with Bendectin was compared with that of 57 other patients treated with a placebo. In this group of 109 patients, there was a favorable response to Bendectin in 94 per cent and to the placebo in only 65 per cent."[2]

Measure Bendectin against your present Rx:

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1. Middleton, T. F.: Postgrad. Med. *24*:699, 1958.
2. Geiger, C. J., *et al.*: Obst. & Gynec. *5*:688, 1959.
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*Traylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61:71-74 (Jan.) 1951.

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GYNECOLOGY

The physiology and clinical significance of the uterine isthmus

Part I. The two-stage intrauterine balloon in the diagnosis and treatment of cervical incompetence

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THE uterine isthmus is a remarkably complex sphincteric segment, the intricate dynamics of which determine important aspects of menstrual and gestational function.[1, 2] With largely prospective methods of investigation, the physiologic and clinical significance of normal and abnormal variations in isthmic tone have been studied in relation to over 400 habitual aborters and over 100 nonaborting control patients. The two-stage intrauterine balloon method, conceived and developed during the course of the study, was preconceptionally employed in the control group to establish isthmic norms and in the habitual abortion group to establish the significance, during pregnancy, of departures from these preconceptional norms. This report shall be primarily concerned with the relationship between impaired isthmic function and cervical incompetence.

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Two-stage intrauterine balloon

The two-stage intrauterine balloon is a device capable of sequential expansion within the corpus, isthmus, and cervix.[3] The in-

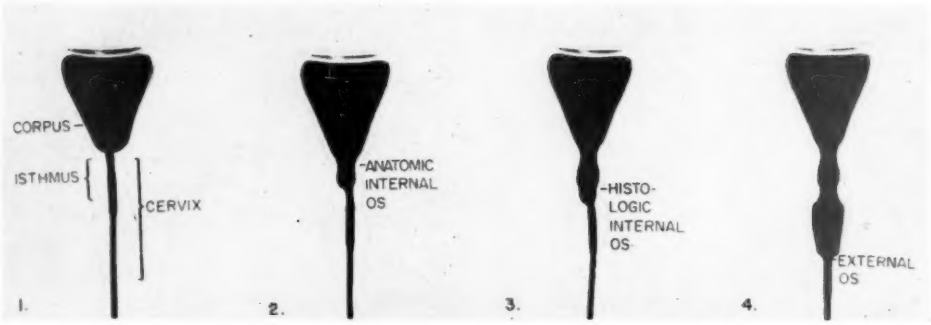


Fig. 1. Dynamics of the two-stage balloon as illustrated by a glass model of the uterus. *1,* The inflated balloon head has filled the corpus. *2,* Peripheral (myometrial) resistance has, with increased filling, resulted in a pressure rise sufficient to effect secondary expansion of the latex neck within the isthmus. *3,* The isthmic segment is completely outlined as additional contrast material produces downward expansion of the latex neck. *4,* Downward expansion is complete when the latex neck has filled the endocervix.

strument consists of an expansile unit attached to a nonexpansile catheter. The expansile unit is comprised of a latex head to which is attached a latex neck. When the unit is inserted into the uterus and radiopaque contrast material introduced into the open end of the system, expansion occurs in two stages. The latex head, having a wider diameter than its latex neck and therefore a lower threshold for expansion, expands first. As the expanding head encounters myometrial resistance the pressure within the entire expansile unit rises. When the pressure reaches the threshold for expansion of the latex neck, secondary expansion occurs within the isthmic-cervical segment (Fig. 1). In the process, not only is delineation of the isthmus and cervix possible, but measurable intraisthmic and endocervical calibers, under known pressures, are obtainable.

The balloon, at its present level of development, remains a research device which for safe use requires specific radiographic and manometric safeguards. Since high orders of intrauterine pressures are developed, a pressure transducer should be used in conjunction with each study. In addition, expansion and descent of the balloon should be observed fluoroscopically in order to detect and correct malposition of the balloon and kinking of the balloon neck. Moreover, unless balloons of varying sizes are used, a significant number of studies will be unsuccessful in patients with enlarged or hypotonic uteri. Revisions in the direction of a larger balloon with lowered pressure gradients of expansion are now in progress although delayed by a change in custom supplier.* The latest revision, after limited clinical trial, appears to obviate many of the problems encountered in preceding models. Until such time, however, as the revised model is more adequately tested and the need for involved safeguards is reduced we shall limit its use to adequately equipped research centers.

Normal variations in isthmic tone. The principal value of the two-stage balloon is its ability to demonstrate the tone and configuration of the uterine isthmus, the constricted area lying between the corpus and cervix (Fig. 2).

Depending upon the phase of the menstrual cycle the normal isthmus is alternately hypotonic, hypertonic, and atonic (Fig. 3). Immediately preceding and during menstruation the isthmic segment is short and relatively atonic. During the early proliferative phase of the cycle there is a gradual increase in isthmic tone, the increase usually being more pronounced in the lower than in the upper isthmic segment (Fig. 4).

*The newly revised experimental models are being supplied through the courtesy of Milex Products. They are not commercially available.

Following ovulation isthmic tone is greatest. Throughout the secretory phase of the cycle the isthmus progressively lengthens and assumes a hypertonic, tubular appearance. Isthmic hypertonia normally persists until the immediate premenstrual period when within a matter of hours prior to menstruation isthmic relaxation occurs (Fig. 5).

Abnormal variations in isthmic tone. In order to establish mathematical standards by which the degree of isthmic tone in a given phase of the cycle could be classified as normal or abnormal, absolute measurements of the isthmic segment were made. The measurements, taken from a standardized projected image of each cineradiographic study were, for purposes of analysis, grouped according to the phase of the cycle in which the given balloon study was obtained. Within each of the matched groupings there was remarkably little variability in the measurements of isthmic length and width of the normal controls. In 13 per cent of 250 unselected habitual aborters (randomly referred to the habitual abortion clinic of the New York Lying-In Hospital on the basis of 3 or more consecutive miscarriages) and in 65 per cent of 150 selected habitual aborters (privately referred on the basis of histories suggestive of cervical incompetence) isthmic width in every phase of the menstrual cycle was significantly greater than in the normal controls. These wider measurements, while significantly abnormal in the menstrual and proliferative phases of the cycle, were most clearly abnormal in the secretory phase of the cycle. Whereas the proportional difference in isthmic width between normal and abnormal during the menstrual and proliferative phases of the cycle was approximately 2:3, the proportional difference in the secretory phase of the cycle was 1:2. Accordingly, differentiation between normal and abnormal is most accurate when the balloon study is performed in the secretory phase.



Fig. 2. Normal isthmus. Note the localized constrictions at the superior (A.I.O.) and inferior (H.I.O.) boundaries of the isthmus, the anatomic and histologic internal ora. These represent the points of maximum resistance during inflation of the balloon and are usually "ironed out" by the time a conventional supine radiograph is obtained following the course of inflation under cinefluorography.

Interpretation is based upon both isthmic contour and isthmic measurements. If the diameter of the entire isthmic segment in the secretory phase of the cycle approaches or exceeds the diameter of the normally more distensible cervical segment the study is judged to be abnormal (Fig. 6). Depending upon the absolute measurements of isthmic width the study is further judged, in terms of degree, to be hypotonic, markedly hypotonic, or atonic.

The hypotonic isthmus and the syndrome of cervical incompetence

If we assume that the primary role of the uterine isthmus is sphincteric in nature; that the cyclic variations in isthmic tone represent normal adaptational changes necessitated by menstruation; and that isthmic hypertonia, occurring as it normally does during the luteal phase of the menstrual cycle, represents the progestational counterpart of a gestational sphincter; it follows that impaired sphincteric function of the isthmic segment in the nonpregnant state might well correlate with impaired sphincteric function during pregnancy. To test this assumption, preconceptional balloon studies were performed on a large group of both selected and unselected habitual aborters who were then closely followed through a pregnancy. Correlations between preconceptional isthmic findings and normal or abnormal vicissitudes of pregnancy were made. Of compelling significance was the close correlation between abnormal isthmic hypotonia in the nonpregnant state and the development of cervical incompetence during pregnancy.

The syndrome of cervical incompetence is characterized by painless, passive dilatation of the cervix culminating in prolapse of the intact membranes. In the absence of surgical intervention secondary uterine contractions then occur and a normal fetus is expelled which soon thereafter dies of immaturity. Fifty pregnancies satisfying these criteria (except that most were surgically



Fig. 3. Cyclic variations in isthmic tone in a normal control. *A*, Proliferative phase (Day 7). The isthmus is patulous but fairly well defined. *B*, Secretory phase (Day 21). The isthmus, 14 days later, is constricted and very well defined. *C*, Menstrual phase (Day 1). The isthmus, 7 days later and 12 hours after the onset of menstrual flow, is physiologically incompetent.

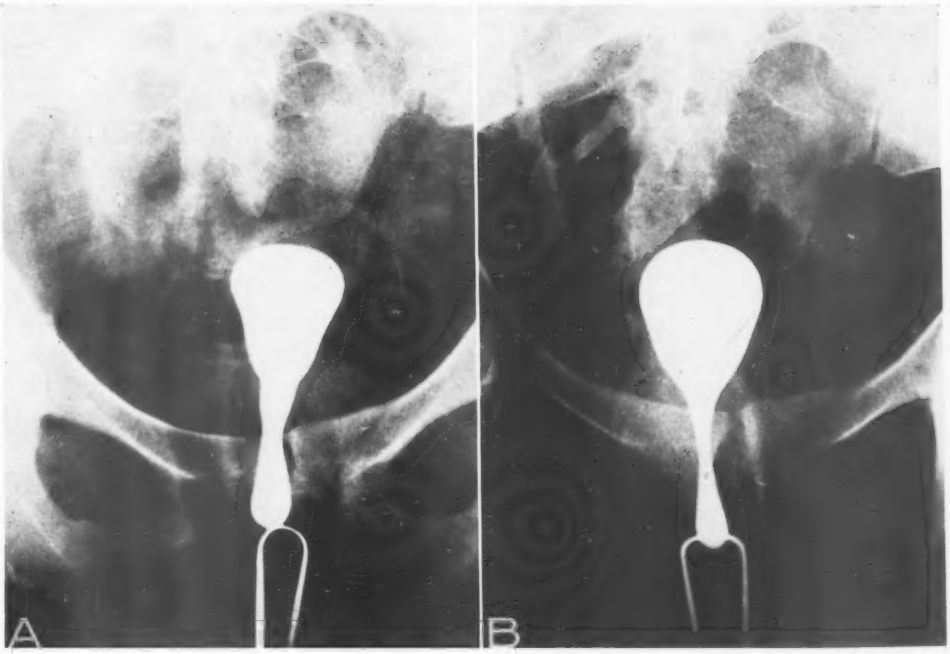


Fig. 4. Normal isthmic changes occurring in relation to the late proliferative and early secretory phases of the cycle. *A,* Preovulatory isthmus (Day 12). Note that recovery of isthmic tone is more notable in the lower rather than the upper isthmic segment, resulting in a funnel appearance. *B,* Postovulatory isthmus (Day 19) in same patient 7 days later. Note increase in isthmic tone which, while occurring throughout the entire isthmic segment, is proportionally greater in the upper isthmic segment. This results in progressive loss of funnel appearance. Also note comparative hypotonia of the corpus.

conserved after prolapse of the membranes) have been studied as to the significance of not only nonpregnant isthmic findings but also as to past history and the advent of premonitory symptoms.

Most of the 50 patients in whom cervical incompetence was observed to develop were seen at weekly intervals, at which times the isthmic-cervical segment was clinically evaluated by means of bimanual examination. Additionally, the patients on each visit were carefully questioned as to any premonitory signs and symptoms. In every instance cervical incompetence was allowed to progress until such time as it was objectively evidenced by prolapsed membranes.

Without exception each of the 50 patients had one or more signs or symptoms during a period of at least 36 hours prior to the time at which the membranes became visible. Not infrequently these signs and symptoms were manifested as long as a week before cervical incompetence was objectively in evidence. The earliest and most frequent sign was a watery discharge which, while usually manifested by excessive perineal moistness, was in some instances sufficient to be confused by the patient with urine. The next most frequent symptom was a vague sense of pelvic heaviness. This was variously described as "carrying low," as pelvic "fullness," or as upper vaginal "pressure." In some instances the above signs and symptoms were associated with a bloody show and, much more rarely, by frank vaginal bleeding. Back ache and uterine cramping did not usually occur until after prolapse of the membranes and even then only after an intervening period of several hours.

The time at which, in a given individual, cervical incompetence occurred in the observed pregnancy when compared with the time at which abortions had occurred in

previous pregnancies was far from consistent. The 50 patients, consisting of 33 primary aborters and 17 secondary aborters, had, prior to the observed pregnancy, experienced a total of 167 miscarriages. Of this number 65 had occurred in the first trimester, 77 had occurred in the second trimester, and 25 had occurred in the early third trimester of pregnancy. Thirty-six of the 50 patients (72 per cent) had had at least one first trimester abortion with 5 having had 2 and 10 having had 3 or more first trimester abortions. Only 5 of the 50 patients (10 per cent) had in previous pregnancies consistently miscarried in the second trimester. An additional 6 (12 per cent) had in previous pregnancies miscarried in the second or early third trimester and 3 (6 per cent) had previously been delivered repeatedly in the early third trimester.

In the 50 observed pregnancies cervical incompetence occurred as early as the fourteenth week of pregnancy and as late as the thirty-second week, the mean having been 20 weeks. Of significance in this connection was the correlation between the degree of abnormal isthmic hypotonia in the nonpregnant state and the time during pregnancy at which cervical incompetence developed. Those patients who on preconceptional balloon studies were found to have the most marked orders of abnormal isthmic hypotonia tended to develop cervical incompetence earliest in pregnancy. Moreover, they tended in the observed pregnancy to have a higher incidence of first trimester bleeding and, in their past histories, to have had a higher incidence of first trimester abortions. Similarly, those patients with less pronounced orders of abnormal isthmic hypo-

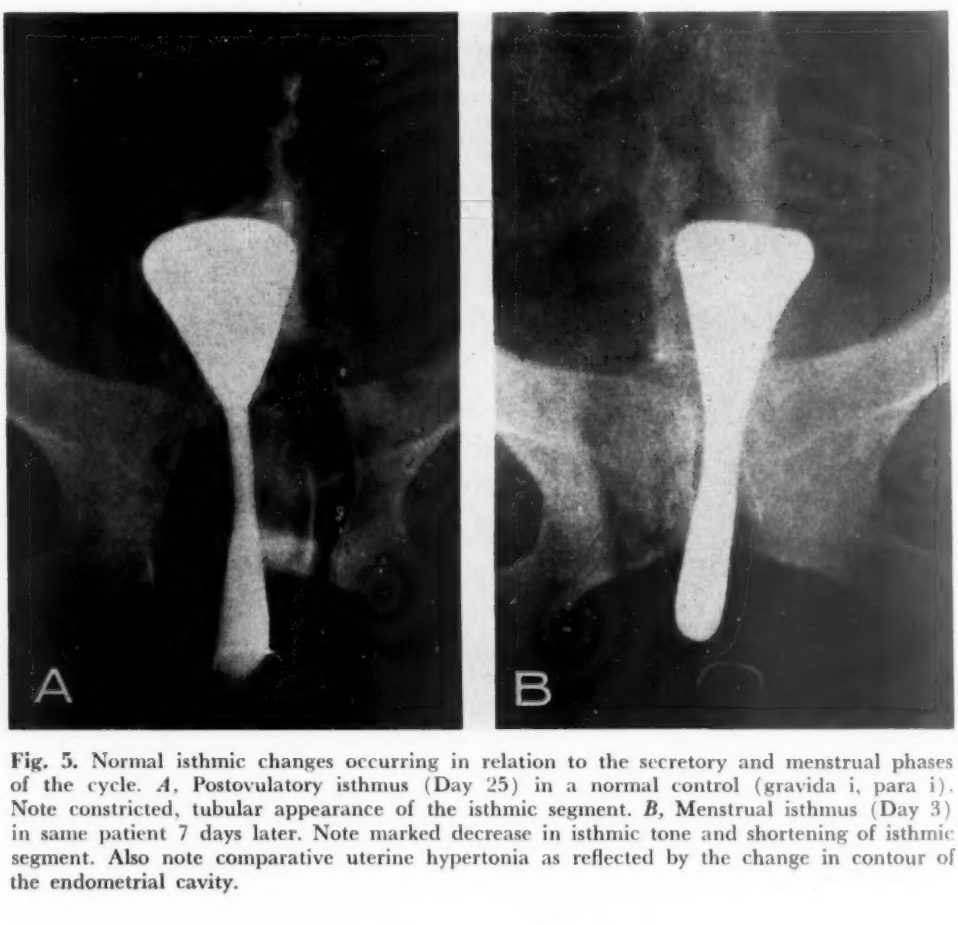


Fig. 5. Normal isthmic changes occurring in relation to the secretory and menstrual phases of the cycle. *A*, Postovulatory isthmus (Day 25) in a normal control (gravida i, para i). Note constricted, tubular appearance of the isthmic segment. *B*, Menstrual isthmus (Day 3) in same patient 7 days later. Note marked decrease in isthmic tone and shortening of isthmic segment. Also note comparative uterine hypertonia as reflected by the change in contour of the endometrial cavity.

tonia tended to develop cervical incompetence later in pregnancy, to have less first trimester bleeding, and to have had the fewest first trimester abortions.

In all but 4 of the 50 patients preconceptional balloon studies were interpreted as being abnormal. The 4 exceptions occurred in patients who developed cervical incompetence in the late second trimester or early third trimester of pregnancy. While false-negative interpretations have occurred we have as yet encountered no instance of false-positive interpretations.

Radiographic documentation of impaired isthmic function during pregnancy

The evidence thus far presented for an isthmic causation of cervical incompetence has been indirect and extrapolative. The close correlation between abnormal isthmic hypotonia in the nonpregnant state and the development of cervical incompetence during pregnancy, coupled with the tendency for patients with the most marked degree of abnormal isthmic hypotonia to abort in the first trimester of pregnancy and for those with the least marked degrees to abort later in pregnancy, only indirectly suggest that the sphincteric weakness associated with cervical incompetence resides in the isthmic rather than in the cervical segment. Direct evidence for this concept has been obtained from hysterograms taken during pregnancy on both control patients and patients in whom cervical incompetence was developing. As was previously indicated, bimanual examinations were performed weekly upon most of the 50 patients who developed cervical incompetence. In most instances, ascending patulousness of the endocervical canal was clinically detectable for a period of several days before isthmic unfolding and cervical dilatation were of a sufficient order to allow prolapse of the membranes.

In order to document this clinical impression and to determine the appearance of the isthmic segment, hysterograms were taken on a few patients who, on the basis of palpable changes in the cervical segment, were thought to be in the incipient stages of cervical incompetence. Fig. 7 is a withdrawal film of such a patient who at the time of hysterogram was 24 weeks pregnant and whose endocervix was becoming increasingly patulous. The film clearly reveals an unfolding isthmus with the membranes down to, but not through, the lowermost portion of the isthmic segment. Three days after this film was taken the membranes prolapsed through the external os, which was by then 2 cm. dilated. Withdrawal films taken during pregnancy on control patients as late as the eighth month have, on the other hand, consistently revealed an intact isthmic segment. Fig. 8 illustrates, again by way of withdrawal hysterography,



Fig. 6. Abnormal isthmic hypotonia. This film was taken during the early secretory phase of the cycle (Day 16) and is remarkable in that there is loss of isthmic tone and landmarks. The diameter of the isthmic segment equals the diameter of the normally much more distensible endocervix. Abnormal isthmic hypotonia in the nonpregnant state correlates closely with the development of cervical incompetence during pregnancy.



Fig. 7. Unfolding isthmic segment in incipient cervical incompetence, This hysterographic withdrawal film of a patient 24 weeks pregnant clearly reveals the determining importance of the isthmic segment in the development of cervical incompetence. The membranes are seen filling the unfolding isthmus and the cervix is partially effaced (note tenaculum on the inferior limit of the cervix). Three days after this film was taken cervical incompetence was objectively evidenced by prolapse of the intact membranes through the cervix which, by then, was almost completely effaced and 2 cm. dilated. Lower isthmic circlage was then performed and 14 weeks later the patient was delivered of a 2,980 gram infant who has since done well.

the intact appearance of the isthmic segment in a gravid control during the thirty-third week of gestation. This particular film was taken 12 hours after loss of the fetal heart tones and was followed by repeat withdrawal films serially taken during the course of induced labor with Pitocin. During the first 6 hours of induction the isthmic segment was radiographically revealed to unfold gradually, during which time the cervix remained relatively unchanged and at the end of which time the cervix rapidly began to efface and dilate.

Just why the isthmus spontaneously unfolds late in normal pregnancy remains a continuing object of inquiry. Hypothesizing the presence in the amniotic fluid of an enzymatic or hormonal substance which might be permeable to the membranes and which, as a transudate, might produce isthmic unfolding and, through the depolymerization of collagen, cervical effacement and dilatation, we have been testing the effect of amniotic fluid on the isthmus and cervix. Amniotic fluid taken from the bulging membranes of 2 of the 4 patients who were found to have normal isthmic tone in the nonpregnant state but who during pregnancy developed cervical incompetence was first used. Balloon studies done on nonpregnant control subjects before and after bathing the intraisthmic and endocervical canals with this amniotic fluid have demonstrated measurable differences in isthmic and cervical tone. Terming this effector substance "proeffacin" we are now testing the effect upon the isthmus and cervix of amniotic fluid taken from patients in various stages of pregnancy and from patients in both premature and term labor. Additionally, the depolymerizing effect of amniotic fluid on the collagenous portions of the cervix is being investigated histologically. Our findings, preliminary as they are, thus far indicate that such an effector substance in the amniotic fluid of patients with manifest cervical incompetence and in active labor at term does exist. Just when in pregnancy this substance appears in the amniotic fluid and to what extent it determines isthmic unfolding and cervical effacement in both cervical incompetence and the end stages of normal pregnancy remains a most provocative area of investigation.

Surgical intervention after prolapse of membranes

Supporting evidence for an isthmic causation of cervical incompetence has been equally compelling in the area of surgical intervention. Following the basic approach described by many other investigators, our initial surgical approach to manifest cervical incompetence was reduction of the herniated membranes followed by what has come to be called cervical circlage.[4-13] While this procedure was often successful there were many attendant disadvantages. Foremost of

these and most pertinent to the problem of etiology was the marked tendency for patients, after cervical circlage, to go into labor from 4 to 8 weeks prior to term. The average birth weight of the infants who lived following cervical circlage was 2,180 grams. Because of the problem of prematurity and the accumulating evidence which implicated the isthmus rather than the cervix in the causation of cervical incompetence, we abandoned cervical circlage in favor of lower isthmic circlage. While this latter procedure was more difficult to perform during pregnancy, the difficulties involved were more than offset by the results. By placement of the purse strings through the uterosacral and cardinal ligaments several problems associated with cervical circlage were obviated. There was no downward slippage of the circumferentially placed suture material; there were far fewer instances of labor in the immediate postoperative period; and, most important, the tendency to premature labor was greatly reduced. Indeed, following lower isthmic circlage the average birth weight of infants delivered (either electively or after the onset of labor) was 2,860 grams.

To date a total of 46 pregnant patients have undergone either cervical or isthmic circlage after prolapse of the membranes through a prematurely dilated cervix. The over-all success rate, in terms of infants who lived, has been 70 per cent. The success rate with cervical circlage (17 patients) was approximately 50 per cent whereas with lower isthmic circlage (29 patients) the success rate was 80 per cent.

The method of delivery following circlage during pregnancy has been, for the most part, from below. Following the onset of labor or, in some instances, on an elective basis at 38 or 39 weeks the sutures have been cut and the membranes artificially ruptured. Labor in most instances has been fast and relatively easy. One patient, who after the sutures were cut developed partial placental separation, and another, who was found to have cephalopelvic disproportion, underwent cesarean section.

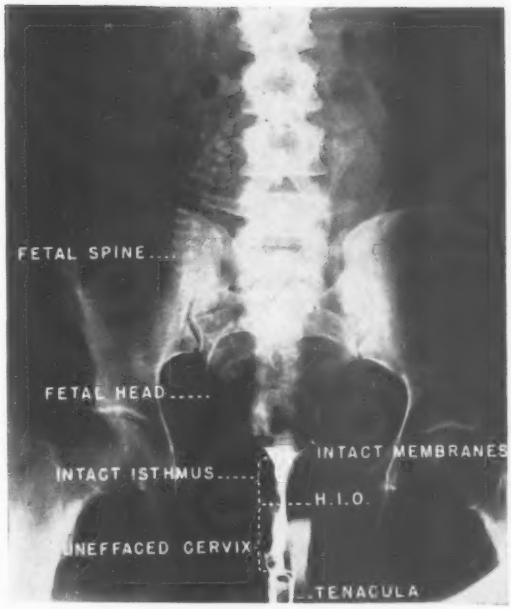


Fig. 8. Intact isthmic segment in the thirty-third week of pregnancy. This hysterographic withdrawal film was taken of a gravid control patient in the thirty-third week of pregnancy 12 hours after the fetal heart sounds were lost. Note the intact isthmic segment and the long, uneffaced cervix. Repeat withdrawal films serially taken during the course of induced labor with Pitocin revealed the isthmic segment to gradually unfold during which time the cervix remained relatively unchanged and at the end of which time the cervix rapidly began to efface and dilate.

Seven patients, subsequent to circlage during pregnancy and delivery from below, were followed through a second pregnancy. In every instance cervical incompetence redeveloped. Thus, in our experience, residual scar tissue after delivery from below is of no avail in preventing the recurrence of cervical incompetence.

Preconceptional restoration of isthmic function

While circlage for cervical incompetence during pregnancy is a very worth-while procedure, it is not without disadvantages. To begin with, some patients, during pregnancy, who develop cervical incompetence will for a variety of reasons be inoperable. If the patient has not been followed closely prolapse of the membranes may go unde-

tected for a sufficient length of time to produce amnionitis, rupture of the membranes, or, secondary to increasing cervical effacement and dilatation, uterine contractions. Additionally, a few patients will in the course of developing cervical incompetence develop bleeding. In the presence of any of these complications operation is contraindicated.

Even in the absence of contraindications the procedure during pregnancy entails certain risks.[14] Excessive blood loss, inadvertent rupture of the membranes, infection, and postoperative labor are possibilities which may occur.

In view of these disadvantages, as well as the fact that patients with markedly abnormal isthmic hypotonia often abort in the first trimester of pregnancy, one of us (E. C. M.) began doing a preconceptional surgical procedure which was based upon balloon study findings and which aimed at the surgical restoration of the sphincteric function of the uterine isthmus. This procedure entails the circumferential placement of purse strings quite high, at the levels of the upper and lower boundaries of the isthmic segment. The sutures are tied over a No. 4 Hegar dilator to avoid excessive constriction of the isthmic segment.

Thus far, 58 patients have undergone this preconceptional procedure. Some of these were patients in whom circlage during a previous pregnancy had failed, others were patients in whom circlage in a previous pregnancy had been successful, the purse strings having been cut to effect delivery from below. The remainder were privately referred patients who in previous pregnancies had been observed to develop cervical incompetence. All, upon balloon study, had abnormal isthmic hypotonia.

To date 36 of these patients have been followed through a pregnancy. Of this number 32 have been delivered of full-term infants and 4 have aborted. Three of the 4 aborted before the eighth week of pregnancy and had no great difficulty in passing the products of conception. The abortive process was somewhat more painful than usual as a result of the placental tissue having been "penciled" out. In only one patient, in whom the placenta separated in the sixteenth week of pregnancy, did it become necessary to undo the operation. After the removal of the sutures the patient aborted without further incident.

In none of the 32 successful cases did labor ensue before the thirty-eighth week of pregnancy. Twenty-nine of the 32 patients underwent elective cesarean section between the thirty-eighth and fortieth weeks of pregnancy and one in the thirty-ninth week of pregnancy after the onset of labor. Two patients, who wanted to be delivered vaginally, were delivered without difficulty after the sutures were electively removed at 38 weeks. All of the infants survived except one who died in the neonatal period from a combination of erythroblastosis and hyaline membrane disease.

The average birth weight of the successfully delivered infants was 3,160 grams. Here again it would appear that the more completely the isthmic segment is surgically reconstituted the less the likelihood for premature labor. As will be recalled, cervical circlage resulted in a high incidence of prematurity, whereas lower isthmic circlage resulted in a relatively low incidence. Since the upper reaches of the isthmic segment are more safely and completely accessible for circlage in the nonpregnant than in the pregnant state, it would seem to follow that the incidence of premature labor would be least after preconceptional isthmic repair.

Technique. Fig. 9 is a schematic representation of the anatomic levels and land-

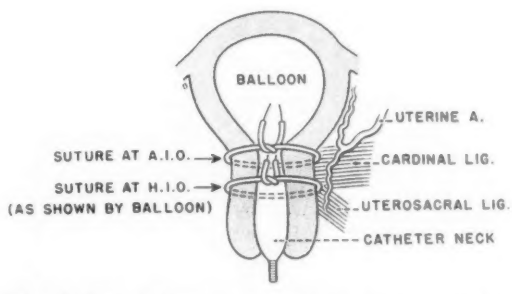


Fig. 9. The balloon as a guide in reconstruction of the isthmus.

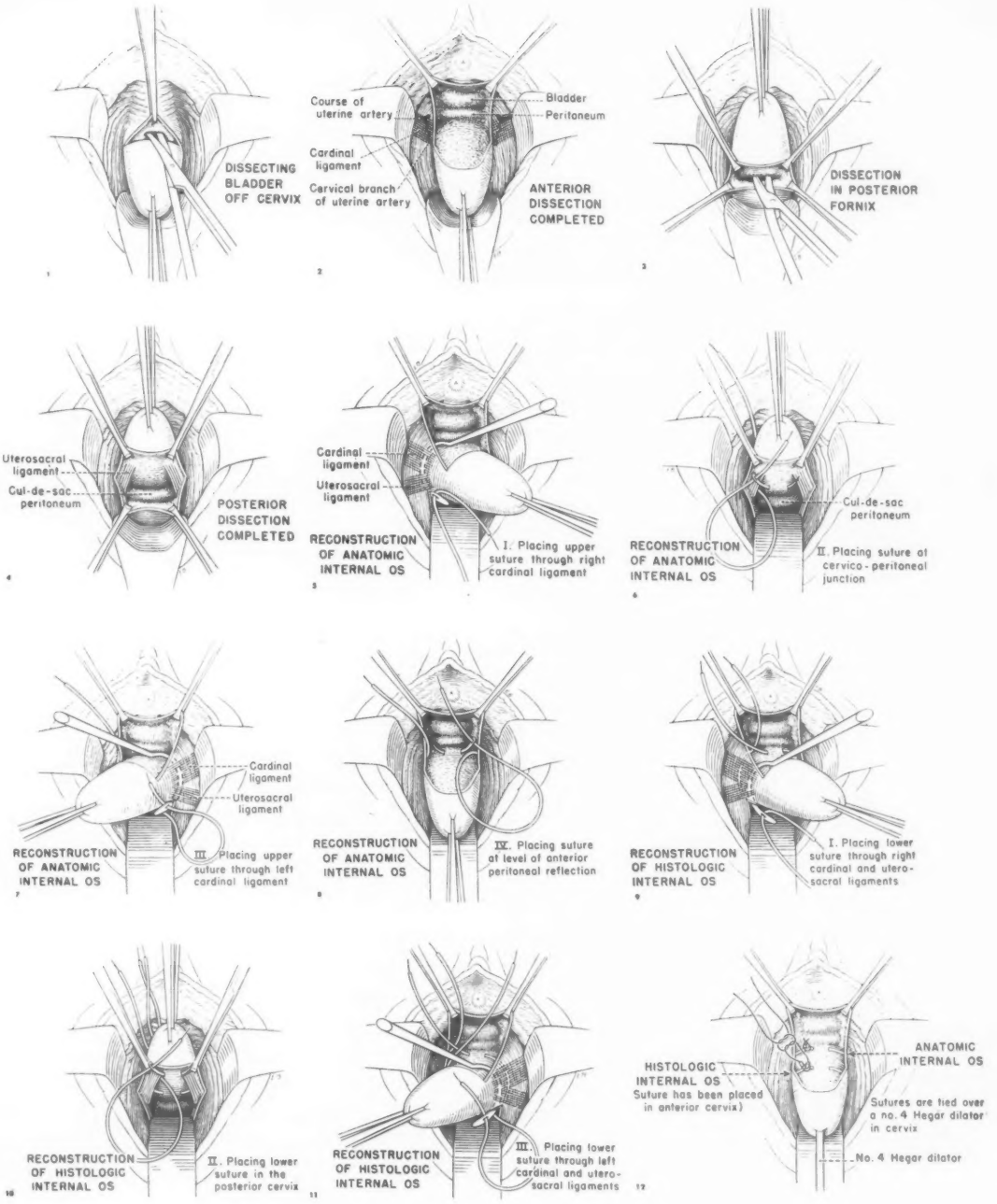


Fig. 10. Preconceptional isthmic circlage.

marks involved in the preconceptional restoration of isthmic function. Prior to operation the individual balloon study is reviewed and used as a guide in determining the upper and lower boundaries of the isthmic segment. The studies are quite helpful in establishing isthmic boundaries, particularly in those patients with congenitally short isthmic-cervical segments.

Because the suture material is fixed laterally by way of superior and inferior tunnels through the cardinal and uterosacral ligaments, small caliber suture material rather than a single ribbon type of suture

is necessary. The use of a ribbon type of suture to embrace circumferentially the entire isthmic segment would entail too extensive an interruption of the insertions of the cardinal and uterosacral ligaments. For the most part we have used No. 2 nylon encased in No. 21 polyethylene tubing. Polyethylene-encased steel wire has also been used, and more recently we have employed braided nylon. While each of the above is satisfactory, the best type of suture material remains to be determined.

In Fig. 10, illustrations *1* and *2* show the dissection of the bladder from the anterior aspect of the cervix. After the vaginal mucosa is incised just above the point where it meets the cervix, the bladder is freed from the cervix by means of blunt and sharp dissection. This must be carried to the peritoneal reflection since this marks the approximate level of the anatomic internal os.

Illustration *2* shows in schematic fashion the relation of the uterine artery to the uterus. There is ample room to place the aneurysm needle between the isthmus and the descending branch of the artery if it is realized that the needle must be placed in close proximity to the isthmic musculature.

Illustrations *3* and *4* demonstrate the posterior peritoneum of the cul-de-sac after the vaginal mucosa has been incised. The posterior peritoneum can usually be elevated by blunt dissection, thus enabling the upper suture to pass just above the insertion of the uterosacral ligaments.

Illustrations *5, 6, 7,* and *8* demonstrate the reconstruction of the anatomic internal os. In illustration *5,* the aneurysm needle, being kept as close to the isthmic musculature as possible, is passed through the right cardinal ligament at the level of the peritoneal reflection. The descending cervical vessels will be lateral to the needle, if the isthmic segment is "hugged." The suture material is threaded through the needle and the needle is withdrawn. Thus, the cardinal ligament provides lateral support.

Illustration *6* shows the posterior support for this suture is obtained by threading it through a round or cutting edge needle and anchoring it in the posterior isthmic musculature. Burial of the suture should be in the midline and as near to the peritoneum as possible.

In illustration *7,* the suture has been threaded through an aneurysm needle which has been passed through the left cardinal ligament in the manner described in illustration *5.* The level of the suture corresponds to that of the opposite side.

In illustration *8,* the suture is again transferred to a conventional needle and anterior support is provided by anchorage in the midline of the isthmic musculature. This should be as close to the peritoneal reflection as possible. Thus the suture supporting the *anatomic internal os* is supported by the cardinal ligaments laterally, and by burial in the isthmic musculature anteriorly and posteriorly.

Illustrations *9, 10, 11,* and *12* demonstrate the reconstruction of the histologic internal os. There are no gross anatomic landmarks to determine the proper level of this suture. Often this can be found on the balloon study. If the histologic internal os does not appear on the study, the supporting suture should be placed approximately 1.5 cm. below the suture supporting the anatomic internal os.

Illustration *9* shows the suture material has been threaded through the aneurysm needle after it has been passed through the lower right cardinal and the uterosacral ligament. Withdrawal of the threaded needle results in the anchoring of the suture on the right.

In illustration *10,* the suture is shown threaded through a curved needle with a substantial bite taken in the midline of the fibromuscular junction between cervix and isthmus. The suture at the level of the anatomic internal os is seen above.

Illustration *11*—as on the right, anchoring is obtained on the left by passing the aneurysm needle through the left cardinal and uterosacral ligaments. The suture material has been threaded through the needle.

Illustration *12* shows the completed operation. A final bite has been taken ante-

riorly at the fibromuscular junction between cervix and isthmus and the lower suture is now anchored in four quadrants. A No. 4 Hegar dilator has been placed in the cervix and isthmus to prevent excessive isthmic constriction when the sutures are tied. If polyethylene tubing is used, it should be tied with a square knot. The tubing distal to the knot is stripped from the nylon sutures which are then tied to prevent slippage. After both sutures have been tied the vaginal mucosa is reapproximated.

Blood loss during the course of the operation is reduced to a minimum if vasopressin[15] is initially injected into the four quadrants of the isthmic cervical segment. The patient may be up the day after operation and she is usually ready to be discharged on the third or fourth day after operation. Coitus should be interdicted for 6 weeks; pregnancy may be attempted anytime after a 2 month postoperative interval.

Thus far we have encountered no instances of infertility following this procedure. Since neither the endocervical nor the intraisthmic canal is surgically involved, this is not surprising. Pregnancy following this procedure requires that both patient and obstetrician be fully cognizant of potential complications. The patient should be appraised of the fact that preconceptional isthmic circlage obstructs the expulsive aspects of premature labor and that, in consequence, she must immediately report to the doctor any sign or symptom such as bleeding, pain, or contractions which might indicate the onset of premature labor. By the same token, the obstetrician must be available to manage such a contingency and, if absent, should arrange for coverage by a colleague thoroughly familiar with the procedure and its possible complications. While we have had no serious complications arise during pregnancy following the preconceptional procedure, it is inevitable that, in time, some will arise.

Conclusion

The close correlation between impaired isthmic tone in the nonpregnant state and the development of cervical incompetence during pregnancy strongly suggests that the isthmus, rather than representing a reserve uterine segment which passively unfolds early in pregnancy, is a functional sphincter of transcendent importance. Indeed, on the basis of our findings, it can be convincingly formulated that the isthmus rather than the cervix is the primary sphincter of pregnancy, that the cyclic variations in isthmic tone in the nonpregnant state represent normal adaptational changes necessitated by menstruation, and that isthmic hypertonia, occurring as it normally does during the luteal phase of the cycle, represents a progestational counterpart of a gestational sphincter which is operative throughout most of pregnancy.

Summary

1. The two-stage intrauterine balloon, a *research* device capable of sequential expansion within the corpus, isthmus, and cervix, is presented, and its application to the preconceptional diagnosis of cervical incompetence is described. Until further modified in the direction of lowered pressure gradients of expansion its use as a clinical tool is not recommended.

2. Cervical incompetence is formulated as occurring in secondary relation to impaired sphincteric function of the uterine isthmus.

3. Evidence is presented which indicates that isthmic tone is essential if a pregnancy is to reach the stages of fetal viability.

4. Preconceptional restoration of the sphincteric function of the uterine isthmus is described. In terms of increased fetal salvage and birth weight it appears to be superior to postconceptional procedures.

5. The responsibility of the physician to the patient following preconceptional isthmic circlage is stressed.

We are greatly indebted to Mrs. Jessie Lockhart, who throughout the course of the study has tirelessly and indispensably served as our x-ray technician.

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Weight, temperature changes, and psychosomatic symptomatology in relation to the menstrual cycle

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WOMEN are known to suffer at least some inconvenience during certain phases of the reproductive cycle and often with considerable mental and physical distress. Woman's awareness of her inherent disabilities is thought to create added mental and in turn physical changes in the total body response, and thus there result problems that concern the physician who must deal with them. These are in both the physiological and psychological areas, with disturbances that may involve physical, mental, and emotional processes. Their satisfactory handling depends a great deal on the physician's knowledge and understanding of the mechanisms operating in the menstrual cycle.[1-5]

There are few reports of sustained and systematic attempts to correlate physical and mental states in woman to the phases of the reproductive cycle. In general, these studies consider a phase, compare segments, or study specific aspects of the cycle. The studies that consider the longitudinal and cross-sectional aspects of the cycle as a whole and the over-all effect are very limited in number. As a result, there is a paucity of information to serve as a base line for controls in projects directed at determining whether or not there are cyclic changes in the physical and mental processes in their relation to each other and to the menstrual cycle.[6, 7]

The need for such studies became apparent when cyclical changes in mentally ill women were evaluated. The changes were in both the behavioral aspects and the physical findings during three specific phases of the menstrual cycle. The changes were observed to be more abnormal than usual and were accompanied by a transient but significant increase in body weight. Similar cyclical changes were found in women amenorrheic as a result of operations, the menopause, or functional disorders. The lack of information in the literature made interpretation of the findings difficult and so limited their value.[11, 12]

This report is a preliminary investigation that attempts to determine the presence and nature of cyclical changes in healthy adult women. It was based on the study of 34 adult women over a period of 3 months and includes determination of the relationship to phases of the menstrual cycle of changes in the daily weight and temperature, and the presence or absence of a selected group of individual signs and symptoms. It was the attempt of this study to establish baseline values that could be used as controls and to gain a better understanding of physical and mental processes and their relationship to processes of the reproductive cycle.

Our findings indicate that there are cyclical changes present that are closely related to each other and have a peak increase

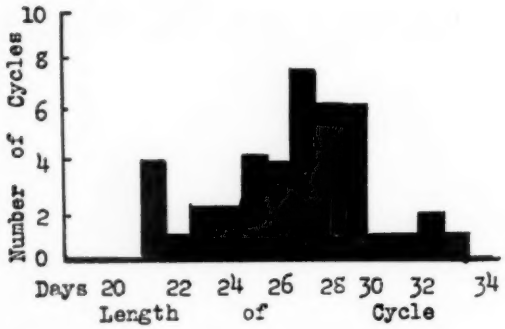


Fig. 1. Length of cycle.

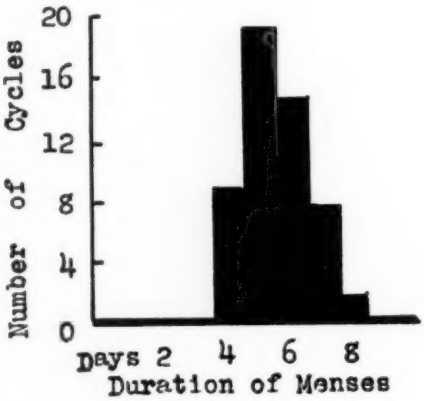


Fig. 2. Duration of menses.

in three phases of the cycle. These changes correspond to the regenerative, ovulatory, and premenstrual phases. Discussion of the method, results, and conclusions are included in this report.*

Method

The study project was presented to approximately 100 student nurses from three hospitals and those interested were encouraged to participate. Graduate nurses were also included. Each subject received a chart for accurate recording of age, marital status, race, parity, gravidity, physical illness, and menstrual history. Participants took their own weight and temperature each morning, using a standard procedure, and recorded them on the chart. Headache, anxiety, fear, restlessness, depression, bloated feeling, abdominal pain, irritability, thirst, hunger, urinary frequency, sexual feeling or desire, increased vaginal mucus secretion, and other symptoms were listed by a designated number and recorded on days they were noted to be present. The day and the hour of the beginning of menstruation and its duration were recorded.

Participants in the study were 34 adult women of whom 26 were student nurses ranging in age from 17 to 21 years of age. There were 8 graduate nurses of whom 4 were 20 to 34 years old and 4 in the 36 to 42 year age range. Thirty were single, 3 married, and one divorced; 3 reported at least one pregnancy. The history indicated that all were free of known pathological lesions. Twenty-nine students and 7 graduates completed the charts for 3 months while 4 completed them for 6 to 8 weeks.

On completion of the study the data were consolidated, including changes in weight and temperature and the symptomatology, by summation of findings for the corresponding days of the cycle with the grouping based on the length of the cycle. This was by having the lowest value of weight and temperature in each cycle represent the base line and assigned a value of zero. The difference for each day was determined and used for summation of composite values. The pounds (broken line) and the degrees Fahrenheit (solid line) in Figs. 4 to 8 represent these summations. In addition, the symptomatology is also represented in graph form including the total number of times and the percentage of participants who reported the individual signs and symptoms.

Each woman menstruated one or more times for a total of 99 times, of which 42 were part of a complete cycle and 37 part of incomplete cycles. Complicating factors excluded 23 incomplete and 7 complete cycles from the calculations.

Results

There was in each cycle a consistent relationship of the weight, temperature, and symptomatology. Each paralleled the other and showed similar changes during the three phases of the cycle. The character-

*Terminology according to Fluhmann.[4]

istics included increase in weight, temperature, and symptoms, with each reaching a peak during three parts of the cycle corresponding approximately to the regenerative, ovulatory, and premenstrual phases. The temperature change lagged behind the weight change, with the peak of the temperature change corresponding closely to the point at which the rate of weight fall was maximal. The weight and symptomatology reach their peaks on the third to the sixth day in the regenerative, the thirteenth to the fifteenth day in the ovulatory, and the twenty-fourth to the twenty-sixth day in the premenstrual phase of the cycle.

The daily weight change had a characteristic pattern for the individual as did the composites of the group. This pattern was based on the relationship of change to the phase, rate of change, duration, and the phases of the cycle in which the subject reached maximum and minimum weight. Composite curves showed peak values at the three points mentioned and are illustrated by Figs. 4 through 8. There was a peak of weight increase reached in 87, 93, and 90 per cent of the cycles for the regenerative, ovulatory, and secretory phases, respectively, each averaging approximately 2½ pounds per individual subject, the average for the premenstrual phase being slightly more than for the other two phases. The phase in which maximum weight was reached varied for the cycle for individual subjects but most frequently was in the premenstrual phase, although it was found at times in the regenerative and ovulatory phases of the cycle.

There was a loss of weight in the intervening periods of the cycle with the minimum following the regenerative phase; this remained low longer than in the other intervals. The minimum weight was reached on the sixth day in the short cycle and on the eleventh day in the longer cycles. The low value following the ovulatory phase was on the thirteenth day for short cycles and nineteenth day for the longer cycles. A low point preceding the regenerative phase was on the second day for the shorter cycles and was on the third day in the longer cycles.

The group listed 13 of the designated signs and symptoms one or more times. There were 2 (6 per cent) who reported one symptom, and 31 (94 per cent) experienced three or more symptoms one or more times in the 3 months. The majority, 22 (66 per

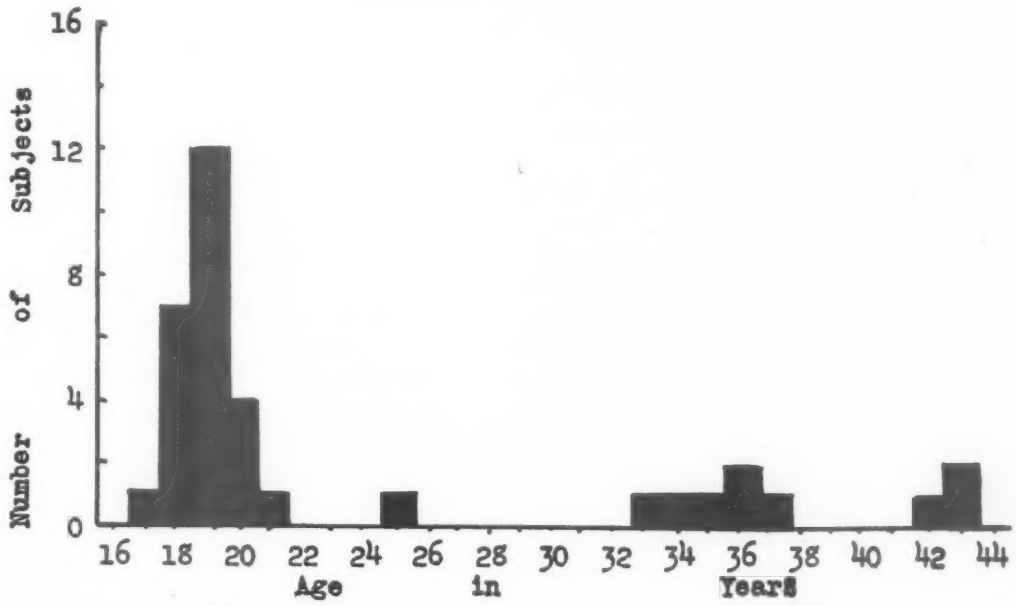


Fig. 3. Age of subjects.

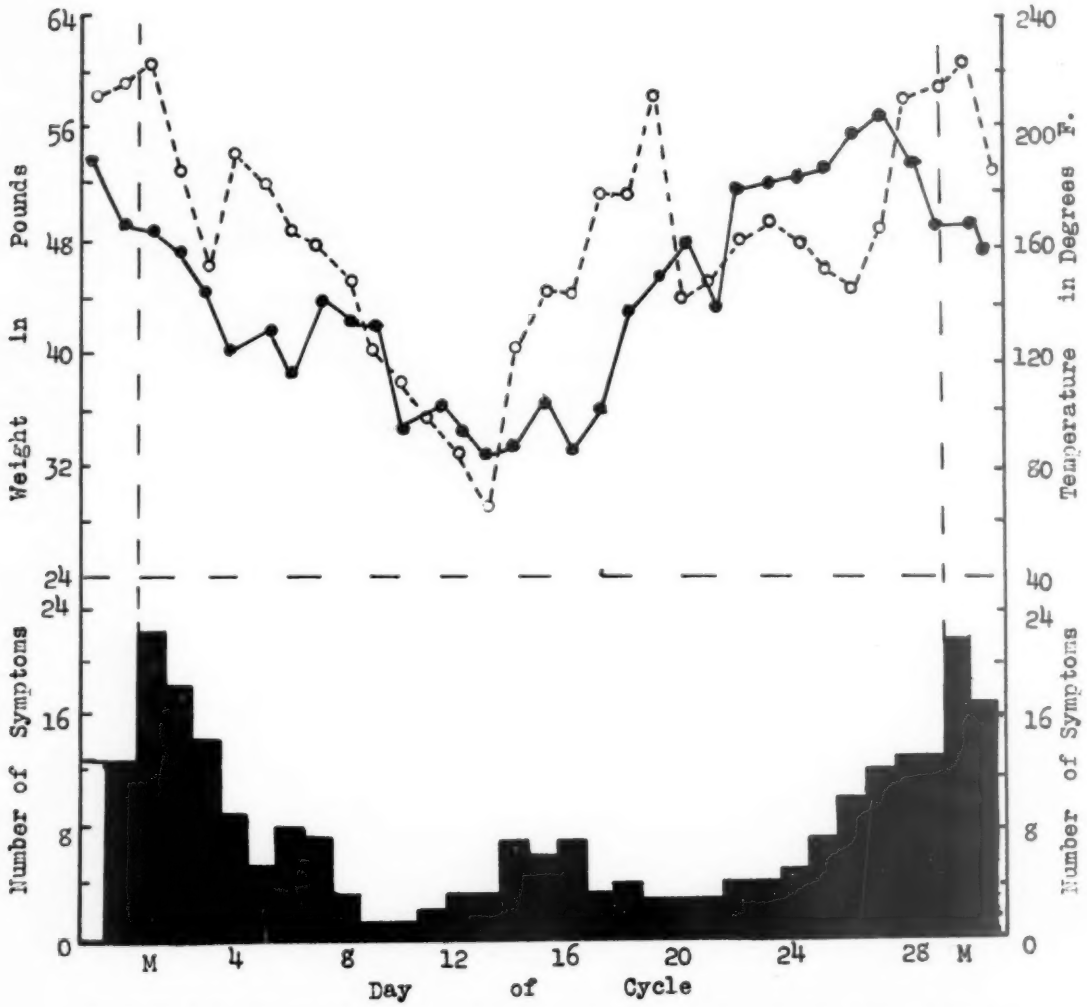


Fig. 4. Includes 20 complete cycles of 17 subjects with duration varying from 27 through 32 days with values corrected to a cycle of 25 days' duration. (Weight is represented by the broken lines and the temperature by solid lines.)

cent), experienced abdominal pain one or more times; 24 (63 per cent) reported headache, 20 (60 per cent) reported irritability, and bloating, depression, thirst, urinary frequency, hunger, and anxiety were registered in decreasing frequency with backache reported by only 7 (20 per cent). Fewer subjects reported headache than abdominal pain, but it was present on more days than was pain, with increasing vaginal secretion second, followed in diminishing order by thirst, abdominal pain, bloating, depression, irritability, anxiety, fear, hunger, urinary frequency, and others.

The majority of the symptoms when considered in a group had a characteristic pattern related to phases of the cycle. The signs and symptoms were such as to increase the discomfort of the individual concerned. The greatest incidence occurred when there was an associated weight increase. This was generally greatest for the premenstrual phase. The increase in the ovulatory and regenerative phases was of a lesser degree. Reduced weight and temperature were associated with a minimum of symptoms. Some of the signs and symptoms had special characteristics and warrant separate consideration.

Increased vaginal mucus secretion and ab-

dominal pain and distress were considered individually because of the difficulty in interpreting their significance in some phases of the cycle. The presence of increased vaginal mucus secretion was difficult to determine during menstruation, thus accounting for the individual consideration. Abdominal pain was found much more frequently on the first 2 days of menstruation and was undoubtedly associated with menstrual cramps, so that its inclusion in the group of symptoms would have been misleading for the purpose of the investigation.

Sexual interest and desire were also considered separately. This was reported on 49 occasions by 9 of the participants. Sixty-four per cent of these instances were noted during the interval between the regenerative and ovulatory phases of the cycle. The remaining instances were ordinarily during the intervals that followed the ovulatory and premenstrual weight and temperature increases. In most instances the increased incidence was noted to be near the point where weight and temperature approached minimum values for the interval concerned.

A relationship of the change in weight, temperature, and symptomatology to the onset of menstruation was noted. On the final day of the cycle there was a fall in the body weight and temperature that continued generally through the first 2 days of menstruation. The number of symptoms was high on the day of onset of menstruation and lower on the day preceding and the day following, but still higher than the incidence on other days of the cycle.

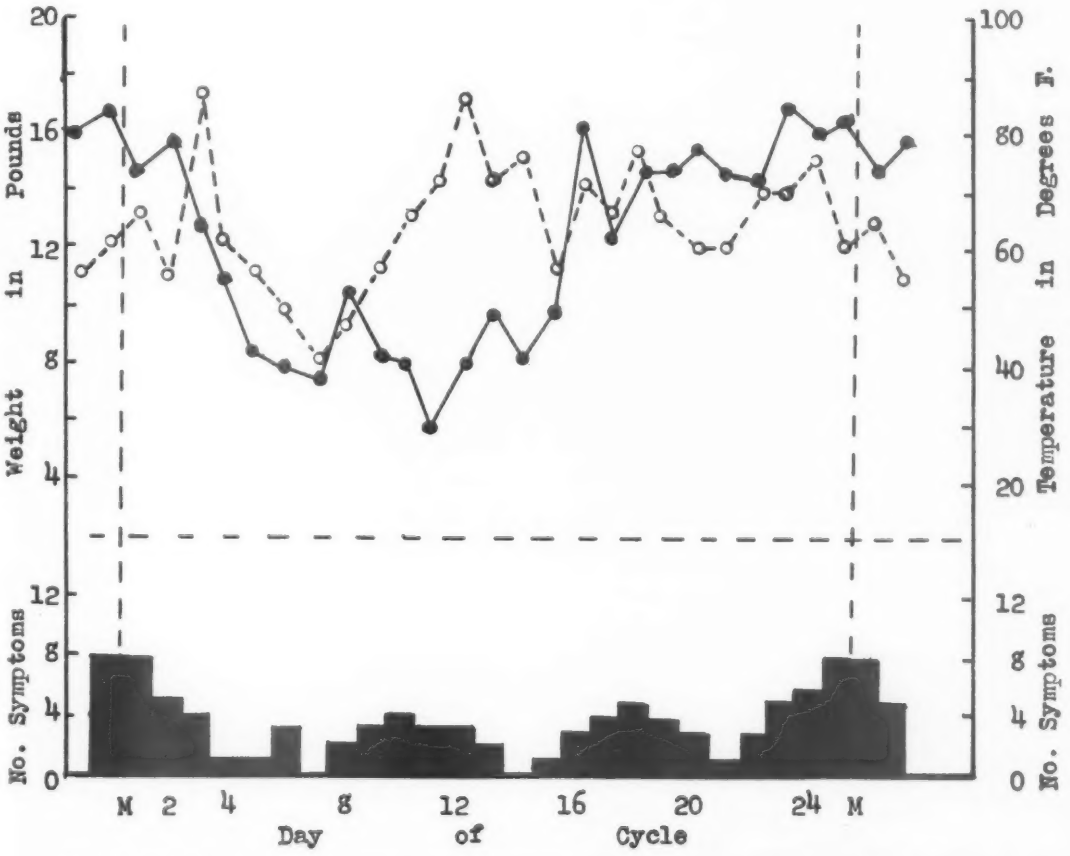


Fig. 5. Includes 7 complete cycles of 5 subjects with duration varying from 24 to 26 days with values corrected to a cycle of 25 days' duration. (Weight is represented by the broken lines and the temperature by solid lines.)

There were findings highly suggestive but requiring further evaluation to be established as significant. Included are those indicating a direct relationship of magnitude of weight and temperature change to incidence and frequency of the symtomatology. The rate of change in the weight and temperature might influence the incidence of the symptoms. The older age group had a greater fluctuation in weight and symptomatology that was significant but application must be restricted to this specific group.

Variations in certain patterns of the composite curves were related to the length of the cycle. The cycles 21 to 23 days in length had a pattern that was similiar to those 26 to 29 days in length, while the 24 to 25 day cycles were similar to the 30 to 33 day cycles. The similarity was primarily in changes closely associated with the onset of menstruation and to the regenerative phase of the cycle.

The pattern of the composite curves suggested periodic fluctuation of the changes in weight, temperature, and symptomatology that was rhythmic in nature and from 4 to 6 days in duration. Generally, there were 5 such periodic fluctuations for each menstrual cycle as indicated by the number of times changes in weight, temperature, and symptomatology increased, reaching a peak, in each. Three of the 5 were the peaks described for the regenerative, ovulatory, and premenstrual phases of the cycle. The other 2 peaks were of lesser magnitude and found in the proliferative phase and in the secretory phase of the cycle, respectively.

Comment

A scientific approach of simple design used in the preliminary study resulted in findings considered significant in fulfilling the intended purpose of the study. Included, as part of the scientific approach, were

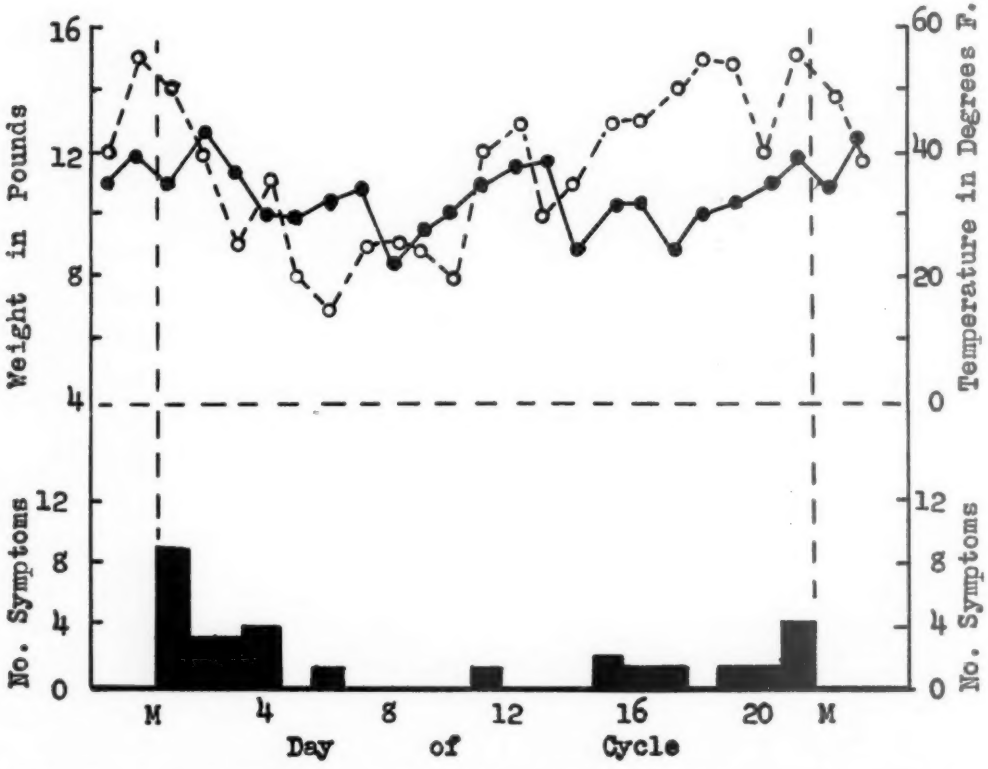


Fig. 6. Includes 7 complete cycles of 5 subjects with duration varying from 21 through 23 days with values corrected to a cycle of 21 days duration. (Weight is represented by the broken lines and the temperature by solid lines.)

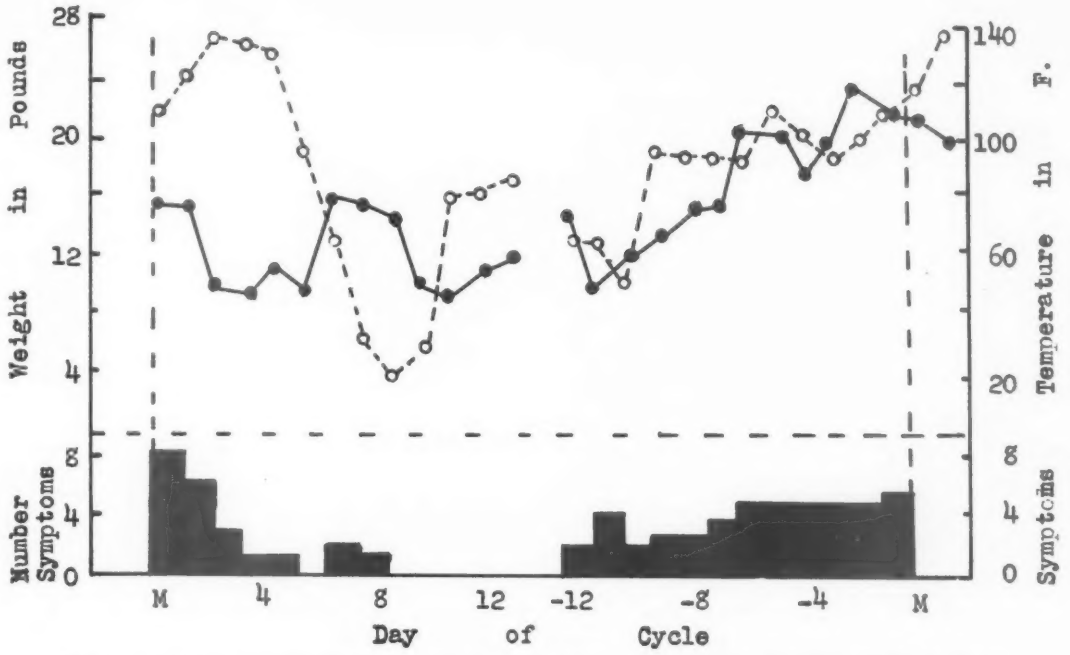


Fig. 7. Includes 12 incomplete cycles in 12 subjects in which the average length of other cycles is less than 34 days in duration. (Weight is represented by the broken lines and the temperature by solid lines.)

determinations selected for specific reasons to help achieve the desired objective. Weight and temperature were used because of: the ease with which each can be measured with a high degree of accuracy; their reported fluctuations during the menstrual cycle; their value in reflecting psychobiological changes; and the established relationship to processes related to the menstrual cycle. The individual signs and symptoms were selected in such a manner that they could be considered as a group which would make possible the detection of any fluctuation related to changes in weight and temperature and to phases in the menstrual cycle. The daily determinations of the weight, temperature, and symptomatology were used to give adequate sensitivity for detecting the cyclical changes thought to have a periodicity of about one third that of the cycle.

The simple approach eliminated some of the difficult problems generally encountered in studies of this type, while others required careful consideration. The calculations and interpretations of the results required the use of a method that eliminated pitfalls that could result in misleading information and conclusions. This became a key factor in giving significance to the study. Avoidance of the changes due to variations in the different cycles, negating those that were a result of rhythmic variations within the cycle, was an important factor in accomplishing this. The periodicity of the rhythmic changes was found to be 6 or seven days; therefore, it was important that cycles differing less than 3 or 4 days be used in the summation of changes for corresponding days. The summation of the cycle in two parts was also a factor that helped reduce the possible error. The summation for corresponding days of one part started with the day of onset of menstruation and then for each subsequent day to midcycle. The summation for the other started with the last day of the cycle and then each preceding day back to midcycle. These techniques proved highly satisfactory in making the necessary calculations.

The application of statistical methods and principles had only limited use because of the many variables in the study. Although

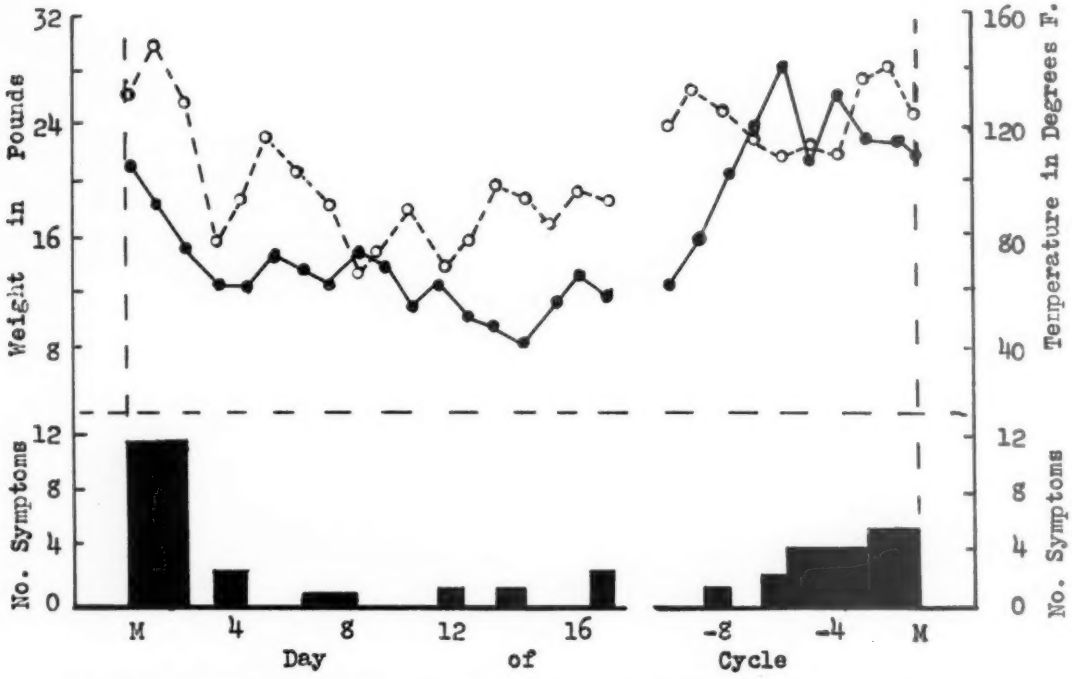


Fig. 8. Includes 12 incomplete cycles in 7 subjects in which the average length of other cycles is greater than 34 days in duration. (Weight is represented by the broken lines and the temperature by solid lines.)

more extensive application would have been desirable, their use was not essential for obtaining experimental evidence needed to establish the authenticity of the study as a suitable scientific experiment. Their use, in addition to the limitations, could have been misleading, giving erroneous and inaccurate results and conclusions. This might have been the case if segments compared approximated the periodicity of the rhythmic changes within the cycle.

The findings of the preliminary study indicate that in women there are fluctuations in weight, temperature, and symptoms that have a cyclic nature and parallel each other, with a periodicity that corresponds to phases of the menstrual cycle. The fluctuations of each increase and reach a peak three times, once each for the regenerative, ovulatory, and premenstrual phases of the cycle. The increase in temperature lags behind that of weight by one to 3 days with a peak close to the time the rate of weight loss is greatest. Changes for the regenerative phase reach their peak from the fourth to the sixth day and are less prominent than in the ovulatory phase where the peak corresponds closely to the day calculated for ovulation. The premenstrual phase has the most prominent fluctuation in both magnitude and duration with the maximum 2 to 5 days before menstruation. The weight and temperature reduction is greatest and of longer duration for the interval that follows the regenerative phase. In this and other intervals the symptomatology is absent or minimal. Temperature and symptomatology have a consistent pattern with a rhythmic characteristic and a periodicity approximating 5 days in shorter and 6 days in longer cycles. Increases in the regenerative, ovulatory, and premenstrual phases of the cycle represent in general corresponding portions of alternate periods. The weight best represents the rhythmic nature of the changes.

It can be readily recognized from the study that further and more extensive investigations in this and related areas are needed before it will be possible to establish the full significance of the findings. There

are observations in related areas and associated with reproductive processes that complement those in this report. Changes in the weight of women are considered by Thorne[8] a result of a fundamental cyclical rhythm alternately involving the retention and release of sodium and water and considered to provide the female with a deep-seated and well-integrated mechanism which may in time of stress be subject to pathological variations. Thomas[7] has observed that a maximal gain in weight is most frequently present during the immediate premenstrual period but may be present at midcycle or following cessation of menstruation. This association, normally of fluid retention with ovulation and menstruation, identifies this as a physiological phenomenon and accounts for the weight increase mentioned. Dalton,[2] comparing 4 day intervals, determined in the different phases of the menstrual cycle the incidence of emergency hospital admissions, suicide attempts, admissions for depression, and admissions for schizophrenia of women with acute mental disturbances. The incidence for each was increased in 3 of the 4 intervals compared and included the intervals just preceding and immediately following menstruation and midway between the onset of two periods. Farris[3] found that the activity, determined by distance walked each day by laboratory technicians and daily work production of women in an ammunition plant, was greater during certain intervals of the menstrual cycle. The increase in walking and work

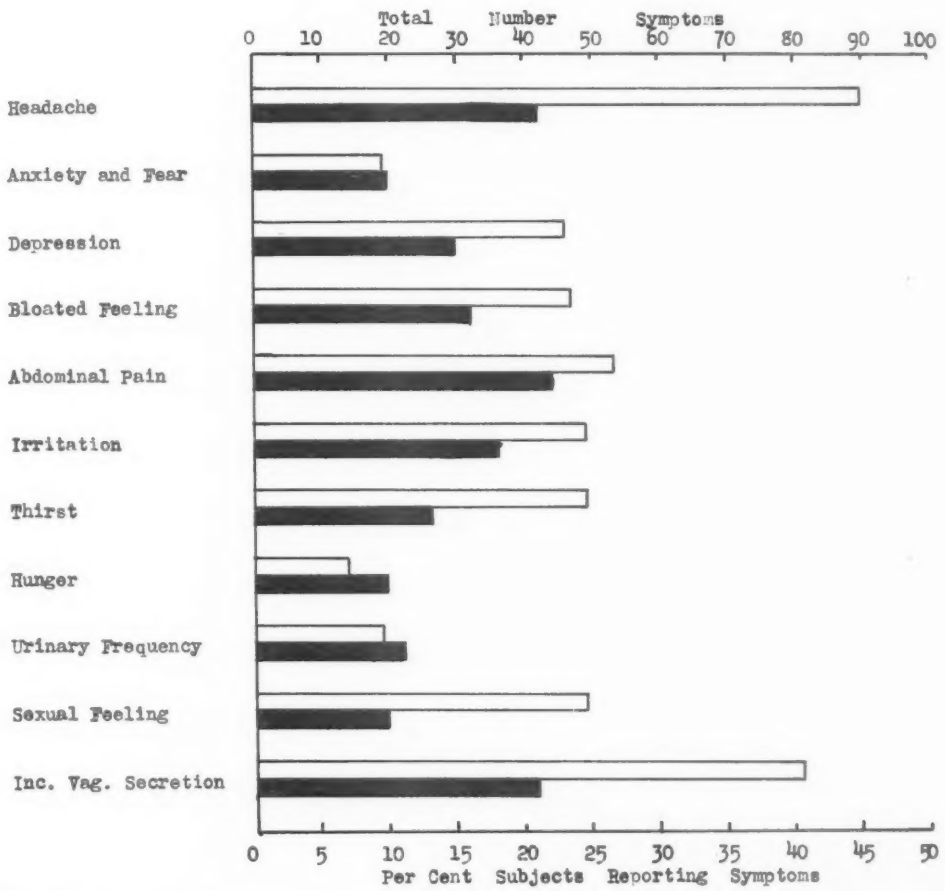


Fig. 9. Diagram represents the total number of times the individual signs and symptoms were reported (unshaded area) and the per cent of the subjects reporting the individual signs and symptoms (shaded bars).

production was found at three regular intervals of the cycle that corresponded closely to the phases of the cycle in which there was found in this study a peak increase in the weight and symptoms. Considering 4 day intervals for weight, symptomatology, activity, and work productivity, there is an increase of each for three intervals, including those just preceding and immediately following the menstrual period and at midcycle. The presence of cyclical fluctuation in both pathological and physiological areas can also be noted by careful examination of data from other studies that do not describe or have as their primary intent evaluation based upon the cyclical nature of changes during the menstrual cycle. Thus, the findings of this study and the others cited suggest a basic cyclical rhythm in the processes related to the reproductive cycle that has a periodicity of one third or less that for the menstrual cycle as a whole.

The results are presented not to prove or disprove anything, but merely to report results considered significant and of value for future studies of these and related processes. Their purpose included establishing baseline values for use as controls and to help in understanding better the cyclical changes in physiobiological processes recognized as being closely related to the mechanisms of reproduction. The findings in the preliminary study indicate certain needs and suggest other areas of exploration. The needs include more extensive studies and evaluations in the areas described in the preliminary project. The evaluations for greater lengths of time would include the use of larger numbers of subjects and comparison of different age periods—childbearing, puberty, the menopause, and the postmenopausal period. Other studies would be made in women during pregnancy, in the postpartum period, and after surgical castration. Similar studies are indicated when there is disease related to reproductive processes. It is hoped that such studies and investigations of the various psychobiological factors will make possible their correlation into a unified concept that adequately covers the longitudinal development as well as the cross-sectional aspect of the psychological and physiological processes related to reproduction. The improved understanding would lead to better preventive and therapeutic techniques as well as open many other areas for needed investigation.

Summary

A preliminary investigation of 34 adult women indicated that the basal body temperature, body weight, and symptomatology commonly associated with menstrual disorders undergo cyclic changes with a periodicity that corresponds closely to specific phases of the menstrual cycle. This included three periods for each cycle in which weight, temperature, and incidence of symptoms increased and reached a peak. These periods corresponded to the regenerative, ovulatory, and premenstrual phases of the cycle. The intervening periods were found to be relatively free of symptoms but the patients had an increase in sexual interest and activity. There were other observations considered suggestive but these require further study for confirmation. The findings, with those reported by others, were discussed and interpreted in terms of the significance for future studies, value for treatment of associated pathological changes, and their significance in regard to future needs and studies.

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Observations on the use of a nonsteroidal estrogen antagonist

I. Cystic disease of the breast

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VARIOUS synthetic and natural steroids have been reported to inhibit or modify the responses of target organs to exogenous and endogenous estrogen. Such steroids include estrogens,[1, 2] progestational substances,[3-8] androgens,[3, 6, 9] adrenal cortical steroids and corticoids,[4, 7, 9-18] and dehydrotachysterol.[19] Impairment of normal response to estrogenic substances is seen after induced dietary folic acid deficiency[20] or subsequent to the administration of aminopterin, a folic acid antagonist.[21, 22]

This report concerns ethamoxytrithetol,* a nonsteroidal compound with the chemical formula 1-(*p*-2-diethylaminoethoxyphenyl)-1-phenyl-2-*p*-anisylethanol (Fig. 1). A free base, this white, crystalline substance has a molecular weight of 419.54 and a melting point of 102° to 104° C. It is soluble in olive oil and alcohol but insoluble in water. The citrate salt, however, is quite soluble in water.

Studies in animals by Lerner, Holthaus, and Thompson[23] have demonstrated that ethamoxytrithetol blocks the response of estrogen target organs to the stimulating action of estrogens. This antagonistic activity has been demonstrated in intact and castrated rats, mice, monkeys, and chicks. The target organs for measuring the degree of estrogen antagonism were the uterus, vagina, and pituitary in mammals and the oviduct in chicks. Findings indicate that:

1. Ethamoxytrithetol antagonizes the activity of both endogenous and exogenous estrogens. It was demonstrated to be an antagonist of both steroidal and nonsteroidal estrogens.

2. Ethamoxytrithetol produces a minimum of uterine growth in castrated and immature rats in moderate doses; larger doses do *not* cause uterine growth.

3. Ethamoxytrithetol decreases pituitary weight in normal rats and prevents estrogen and castration induced pituitary hypertrophy.

4. Ethamoxytrithetol does not produce uterine growth in immature rabbits nor does it antagonize the progestational activity of progesterone.

5. Ethamoxytrithetol completely prevents the elevation in phospholipids and inhibits the oviduct weight increase in 65 per cent of baby chicks given daily estradiol.

6. Ethamoxytrithetol produces no signs of toxicity in animals in doses up to 3.0 Gm. per kilogram of body weight, other than a minor degree of diminished food consumption and subsequent weight loss. No hematologic changes have been evident in serial examinations.

7. Ethamoxytrithetol in doses of 40 mg. per kilogram of body weight prevents menstruation in monkeys and decreases the per cent of cornified vaginal cells.

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**MER-25, provided by the Medical Research Department, The Wm. S. Merrell Co., Cincinnati 15, Ohio.*

8. Ethamoxytrithetol is not androgenic as evidenced by its failure to increase the weight of the seminal vesicles and ventral prostate in castrated male rats.

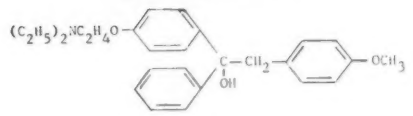
Estrogen is known to be the major stimulant of epithelial growth in the mammary gland. Its administration to immature or castrated animals in which the mammary gland is still rudimentary causes the epithelium to proliferate and develop a duct system with glands identical to those of normal mature animals. The continued administration of large doses of estrogenic substances to normal animals results in a variety of types of epithelial proliferation in the mammary glands, depending on the species and upon the particular strain utilized.[24] The use of estrogenic substances in both male and female human subjects has provided abundant evidence confirming the stimulative effect observed in the mammary epithelium of animals. Exogenous estrogen induces mammary epithelial growth in human female castrates and occasionally results in mastodynia. Bilateral oophorectomy in ovulating females uniformly results in relief from mastodynia associated with cystic disease and diminution in the size of breast masses. The morphologic pattern of chronic cystic mastitis has never been reported in human or animal experimentation in the absence of estrogen stimulation. Conversely, chronic cystic mastitis has been produced in both humans and animals by the administration of excessive, prolonged estrogenic substances.[25] It is reasonable to conclude, therefore, that this lesion owes its genesis, at least in part, to the effect of estrogenic hormones.

The present study

The present study was designed to determine the effects of ethamoxytrithetol in patients with microscopically proved cystic disease of the breast who complained of mastodynia and recurrent masses. Ethamoxytrithetol was administered to 25 patients to antagonize endogenous estrogens.

The patients were between the ages of 32 and 50 and all had had mastodynia for at least one year. They were seen at intervals of 2 weeks during therapy in the outpatient department and wards of the Free Hospital for Women and in my private practice. Three patients (Nos. 1, 8, and 15) had undergone previous hysterectomy and unilateral salpingo-oophorectomy for benign disease, the normal ovary having been spared at operation. Eleven patients had had two previous breast resections and 2 patients had had three separate excisional biopsies prior to ethamoxytrithetol therapy. Most had been treated with testosterone propionate, methyltestosterone, or diuretics. All except Nos. 1, 8, and 15 had normal menstrual periods before treatment. Examination prior to ethamoxytrithetol therapy revealed diffuse nodularity in the upper outer quadrant of both breasts and an occasional discrete, large, mobile cyst.

Ethamoxytrithetol



1-(p-2-Diethylaminoethoxyphenyl)-1-phenyl-2-p-anisylethanol

Fig. 1.

Two target organs, the mammary epithelium and the vagina, were studied for effects of estrogen antagonism. The criteria used to evaluate the effects of ethamoxytrithetol were (1) subjective observations of the patients and (2) objective examination of the involved areas. Each patient was asked to describe mastodynia as: improved, unchanged, or worse. Four patients had daily (Monday through Friday) vaginal smear determinations for cornification index. Three patients had biopsies of breast tissue following ethamoxytrithetol therapy.

The optimum daily dose of ethamoxytrithetol is 1.0 to 2.0 Gm. or 20 to 25 mg. per kilogram (as estimated from animal studies). To allow the patients to become accustomed to the drug, a starting dose of 250 mg. was given once or twice daily for one week. The dose was then increased by 250 mg. per week until the desired dose was reached.

Five of these patients were given a placebo substitute at one time during their treatment. Safety data were obtained from 5.

Ethamoxytrithetol was originally supplied in gelatin capsules containing the free base; but, because of nausea, anorexia, and occasional vomiting, enteric-coated, sustained release tablets were prepared (MRD-531). A later modification (MRD-531-A) provided for sustained release of the medication without enteric coating. These changes resulted in improved tolerance of the medication.

Results

The results of treatment of 25 patients with cystic breast disease who were given varying amounts of ethamoxytrithetol, MRD-531, and MRD-531-A are reported in Table I. Only 3 of the 25 patients (Nos. 9, 18, and 22) did not experience relief from breast pain while receiving therapy, despite considerable objective change in breast size and diminished nodularity. Testosterone similarly did not provide symptomatic relief for these patients. A placebo substitute did not effectively relieve pain in any of the 5 patients tested. Several patients who received therapy intermittently noted relief of pain only when ethamoxytrithetol was being administered and recrudescence of pain and breast nodularity during interims without therapy. No uniform change in the vaginal cornification index was noted in patients who were still actively menstruating. In one patient (No. 8), who had had a previous hysterectomy and unilateral salpingo-oophorectomy, a definite decrease in the percentage of cornified cells was noted during therapy with ethamoxytrithetol. (Subsequent removal of the remaining ovary showed cortical stromal hyperplasia and multiple cystic follicles.)

Severe side effects were observed in 2 pa-

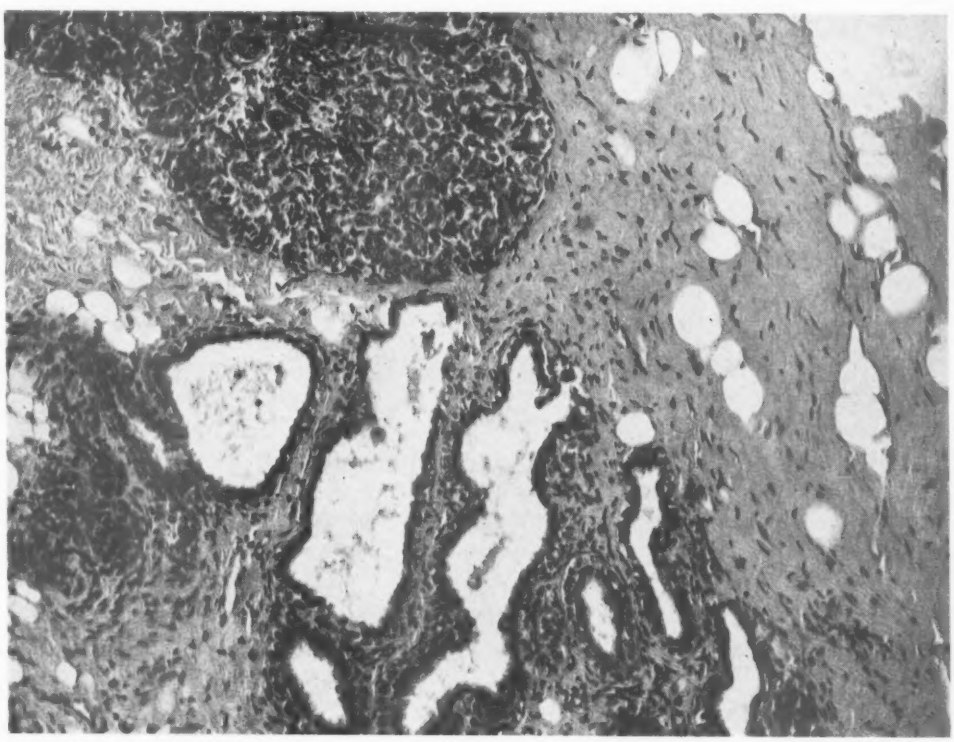


Fig. 2. Patient 9. Photomicrograph showing chronic cystic mastitis with sclerosing adenosis and intraductal hyperplasia. The duct at the upper left is filled with active epithelium. A similar mass had been excised from the opposite breast in 1951. (Original magnification ×150.)

Table I

Patient	*Form of drug**	*Dose*	*Effect*	*Side effects*	*Remarks*
1	Ethamoxytrithetol	1.0 Gm. daily for 33 days	No breast soreness while taking drug	None	Hysterectomy and unilateral oophorectomy in 1953
2	Ethamoxytrithetol	1.5 Gm. daily (Day 6 through Day 26)	Improved during 5 cycles of treatment	None	
3	Ethamoxytrithetol	1.5 Gm. daily (Day 1 through Day 28)	Improved during 3 cycles of treatment	None	Patient felt better, "less tired"; resection after treatment showed benign cyst
4	Ethamoxytrithetol	1.5 Gm. daily (Day 10 through Day 26)	Improved during 2 cycles of treatment	None	Pregnancy 1 month after stopping treatment; delivery August, 1958
5	Ethamoxytrithetol	1.0 Gm. daily (Day 6 through Day 26)	Improved during 7 cycles	None	Pregnancy 2 months after stopping treatment; delivery, September, 1958
	Placebo		No effect		
6	MRD-531	1.5 Gm. daily for 90 days	Improved during treatment	None	
	Placebo		No effect		
7	Ethamoxytrithetol	1.5 Gm. daily (Day 18 through Day 26)	Improved symptomatically not objectively	Nausea	Breast resection after 3 months of treatment
8	Ethamoxytrithetol and MRD-531	1.5 Gm. daily	Improved	Insomnia, anorexia-libido, nightmares	Hysterectomy, unilateral oophorectomy in 1940
	Placebo		No effect		
9	Ethamoxytrithetol	1.5 Gm. daily (Day 12 through Day 28)	Unimproved	None	
10	MRD-531	1.0 Gm. daily for 3 months; repeated for 6 months	Improved	None	Recurrent pain after 3 months of treatment; re-treated beginning January, 1959
11	MRD-531	1.5 Gm. daily for 3 months	Improved	Slight nausea	3 previous breast resections
	Placebo		No effect		
12	MRD-531	1.0 Gm. daily for 3 months	Improved	None	3 previous breast resections
13	MRD-531	1.0 Gm. daily for 3 months	Improved	None	Irregular uterine bleeding 2 months after cessation of treatment; curettage
14	MRD-531	1.0 Gm. daily for 3 months	Improved	None	2 previous breast resections
15	Ethamoxytrithetol	2.0 Gm. daily for 2 months	Improved	Slight nausea, "tired feeling"	2 previous breast resections; hysterectomy and unilateral oophorectomy 1944
	Placebo		No effect		
16	MRD-531	1.0 Gm. daily for 2 months	Improved		
17	Ethamoxytrithetol	0.8 Gm. daily (Day 12 through Day 28)	Improved		

Table I—Cont'd

Patient	*Form of drug**	*Dose*	*Effect*	*Side effects*	*Remarks*
18	MRD-531	1.0 Gm. daily	Improved (objectively)	Nausea, depression	Pain continued but lumps became much smaller
19	MRD-531-A	0.25 Gm. to 1.0 Gm. in 4 weeks; 1.0 Gm. daily for 3 months	Improved	None	
20	MRD-531	0.25 to 1.0 Gm.; 1.0 Gm. daily for 5 months	Marked improvement	"Tired feeling"	
21	MRD-531	0.25 to 0.75 Gm. daily for 4 months	Improved	None	2 previous resections for cystic disease
22	MRD-531	0.25 to 0.75 Gm. daily for 2 months	Not improved	(?) Irregular bleeding	Possibly delayed ovulation
23	MRD-531	0.25 to 0.75 Gm. daily for 2 months	Improved and noted recurrent pain when discontinued	None	
24	MRD-531-A	0.25 to 1.0 Gm. daily for 3 months	Improved; noted disappearance of 1.5 cm. cyst	None	
25	MRD-531-A	0.25 to 1.0 Gm. daily for 3 months	Improved	None	

*Ethamoxytrithetol is supplied as capsules containing the free base. MRD-531 is supplied as enteric-coated, sustained release tablets of the free base. MRD-531-A is identical to MRD-531 except that the tablets are uncoated.

tients. Patient 7 noted nausea and epigastric distress soon after ingestion of ethamoxytrithetol capsules but tolerated the enteric-coated medication without difficulty. Patient 8 described insomnia, anorexia, and nightmares. Patients 7, 11, and 15 noted slight transient nausea and Patient 18 described nausea and a depressed feeling. It is possible that the transient nausea is due to an estrogen effect which occurs when the medication is initiated at a lower dose level. A "tired feeling" was described by Patients 15 and 20, and Patient 22 complained of an episode of irregular vaginal bleeding, possibly associated with the drug. Patient 8 also noted a marked increase in libido which occurred within 48 hours of the ingestion of ethamoxytrithetol. This complaint had been noted in an earlier study when large doses of the original material (ethamoxytrithetol) were given but was not seen following the administration of the sustained-action tablet. Hematologic studies (red cells, white cells, platelets, hemoglobin), nonprotein nitrogen, and liver function tests were normal in 5 patients after 4, 8, and 16 weeks of therapy.

A few representative clinical histories are given below to emphasize the fact that many of these patients prior to treatment with ethamoxytrithetol had recurrent mastodynia and "lumpy breasts" in spite of various forms of therapy, including breast resections.

Case reports

Patient 2. A 32-year-old Negro woman was seen in December, 1957, because of severe bilateral, progressive mastodynia. Because of cystic disease a bilateral breast resection had been performed in 1952 which resulted in relief of pain until 1955. During 1955 and 1956, treatment for



Fig. 3. Patient 9. A higher power view of an adjacent area from the same resected breast tissue shown in Fig. 2. This shows the large epithelial bud pouting into the lumen of a duct. There is active mitotic activity and nuclear crowding. (Original magnification ×200.)

recurrent mastodynia, including methyltestosterone, diuretics, breast support, and codeine, provided only partial relief of the pain. Examination in 1957 revealed diffuse nodularity in the upper quadrants of both breasts but no dominant lump. Therapy with ethamoxytrithetol was begun in December, 1957, with a 500 mg. dose three times daily from the sixth through the twenty-sixth day of the menstrual cycle. There was progressive pain relief and diminution in the size of the breast masses; and after 6 months of consecutive, cyclic therapy, the patient was symptom free and most of the "lumpiness had disappeared. There was no alteration of menses. Upon examination in September, 1958, the breasts were found to be relatively soft and the patient had no complaints. A re-examination in April, 1959, revealed no change in this situation.

Patient 5. A 24-year-old white woman was seen in March, 1957, because of severe mastodynia associated with cystic disease of the breast. A resection of the left breast in 1956 had resulted in only temporary relief. The specimen revealed microscopic changes typical of cystic disease. Examination of the breasts in March, 1957, revealed tenderness and diffuse, "shotty" nodules in both upper outer quadrants without a dominant lump. Ethamoxytrithetol was administered in a dose of 0.8 to 1.0 Gm. daily from the tenth through the twenty-fifth day of the menstrual cycle and was continued from March until September, 1957. Marked subjective and objective improvement was noted after the second month of therapy. A placebo was substituted in October and November, 1957; but because of a recrudescence of pain and nodularity, ethamoxytrithetol was restarted in December, 1957. During therapy the menstrual periods continued normally and pregnancy occurred in February, 1958. Therapy was discontinued and the patient was delivered normally in October, 1958. Follow-up examination in March, 1959, revealed that the patient was free of pain and both breasts were only slightly nodular.

Patient 8. A 47-year-old white woman was seen in February, 1958, for recurrent mastodynia. A hysterectomy and left salpingo-oophorectomy had been performed in 1940 for dysmenorrhea

and irregular flowing. Resections of the left breast were performed in 1953 and 1957, and in each case microscopic examination revealed severe chronic cystic mastitis with intraductal papillomatosis, lobular hyperplasia, and anaplasia of the lining epithelium. A vaginal smear at the time of the second breast resection showed "hyperestrinism."

The patient was hospitalized on March 19, 1958. Examination at this time revealed diffuse nodularity in the upper outer quadrants of both breasts without a dominant mass. Pelvic examination revealed a cystic right ovary approximately 5 by 5 cm. in diameter. MRD-531 was administered according to the following dose regimen: 250 mg. every 6 hours for 48 hours, then 500 mg. every 6 hours for 72 hours. Slight nausea was experienced after the dose was increased but this was controlled with chlorpromazine. During the treatment period, subjective improvement of mastodynia was reported. On May 29, 1958, a right salpingo-oophorectomy was performed. The ovary measured 4 by 5 cm. and was studded with multiple small cysts, some of which contained dark fluid. The walls of these cysts were lined with yellow streaks. Microscopic examination revealed cortical stromal hyperplasia, cystic follicles, and luteal cysts.

Daily vaginal smears were obtained during the control and treatment periods with ethamoxytrithetol. Microscopic examination of these smears indicated an antiestrogenic effect, with a notable decrease in the degree of cellular cornification (Table II).

Patient 9. A 44-year-old white woman was seen in January, 1957, because of mastodynia and "lumpy breasts." Past history revealed that a 2 cm. mass had been excised from the right breast in 1951, the pathologic diagnosis being "chronic cystic mastitis." Examination in January, 1957, revealed extensive irregular nodularity in the left breast with a probable dominant mass. This mass was excised and microscopic examination revealed "chronic cystic mastitis with sclerosing adenosis and intraductal hyperplasia" (Figs. 2 and 3). The patient obtained relief for



Fig. 4. Patient 9. Photomicrograph of an area of breast tissue removed at the termination of therapy with ethamoxytrithetol (1.5 Gm. daily from July 1, 1957, until Sept. 5, 1957). The resected area was immediately adjacent to the site resected previously. Note single or double layer of relatively inactive epithelium and lack of cellularity of the stroma. (Original magnification ×150.)

only 3 months and returned in April, 1957, because of pain in the right breast. Ethamoxytrithetol (800 mg. daily from day 12 to day 28 of the cycle) did not provide symptomatic relief. Methyltestosterone was administered for one cycle but this also did not affect the pain. It was then decided to administer ethamoxytrithetol for 60 days and proceed with another breast resection. Accordingly, the patient was given 1.5 Gm. ethamoxytrithetol from July 1 until Sept. 5, 1957, at which time a resection of the right breast was performed. Microscopic examination of the specimen revealed a moderate degree of chronic cystic mastitis with apocrine metaplasia. Fig. 4 compares the biopsy of the breast resection in September, 1957, with that of January, 1957. The patient was last seen in October, 1958, at which time she was asymptomatic.

Patient 11. A 45-year-old white woman was seen on Sept. 14, 1958, because of recurrent mastodynia with premenstrual aggravation. Three previous breast resections had been performed for the same complaint: (1) October, 1955—resection of left breast, "chronic cystic mastitis with sclerosing adenosis and intraductal hyperplasia"; (2) April, 1957—bilateral breast resection, "chronic cystic mastitis with sclerosing adenosis, intraductal hyperplasia with intraductal papillomatosis"; (3) April, 1958—bilateral breast resection, "chronic cystic mastitis with sclerosing adenosis."

In September, 1958, the patient was again experiencing premenstrual breast tenderness, and examination revealed nodularity. A trial of therapy with MRD-531 was elected and after 4 weeks of therapy the patient noted relief of pain. Treatment was continued for a period of 6 months, during which time marked improvement occurred. The medication was discontinued in March, 1959. An added observation by the patient was that during the time of administration of MRD-531 she noted complete subsidence of "hot flushes and sweats."

Patient 12. A 45-year-old white woman was seen on Nov. 4, 1958, because of "tender breasts." She had had resections for chronic cystic mastitis in 1951, 1952, and 1956. Examination in November, 1958, revealed diffuse nodularity in both breasts and a 4 by 2 cm. tender, discrete thickening beneath the biopsy scar on the right. MRD-531 was started on Nov. 4, 1958, with the following dose regimen: 250 mg. daily for one week, increasing by 250 mg. daily each week until 1.0 Gm. was being administered. By Dec. 9, 1958, moderate improvement had been noted and by Jan. 20, 1959, the subjective result was classified as excellent and both breasts were less nodular. Therapy was discontinued for one month with a prompt recurrence of symptoms. On April 14, 1959, MRD-531 was restarted and within 3 weeks marked improvement was again observed. At the present time she is being continued on 6 consecutive months of therapy.

Table II

Date	*Cornified cells (%)*	*Precornified cells (%)*	*Basal cells (%)*
Control			
March 19	90	10	0
March 20	90	10	0
Treatment			
March 23	70	30	0
March 26	68	32	0
March 27	51	49	0

Patient 14. A 34-year-old white woman was seen on Oct. 22, 1958, because of severe mastodynia. Breast resections had been performed for chronic cystic mastitis in 1951, 1954, and 1958. Examinations of the tissue removed at the last resection (which was bilateral) revealed extensive cystic disease with sclerosing adenosis and intraductal hyperplasia. MRD-531 was administered (750 mg. daily) from Oct. 22, 1958, until March 9, 1959, with marked relief of breast symptoms. Endometrial biopsies were normal during the luteal phase of the cycle on two separate occasions while the patient was receiving therapy. Because of the notable improvement, therapy was continued until July, 1959.

Patient 15. A 41-year-old white woman was seen on June 16, 1958, because of recurrent mastodynia. A hysterectomy and unilateral salpingo-oophorectomy had been performed in 1944 for benign uterine disease. In 1956 a right breast resection had been done for "chronic cystic mastitis" and in 1957 a bilateral resection had been performed because of recurrent pain and a discrete 2 by 2 cm. nodule in the right breast. The specimen showed: "chronic cystic mastitis with sclerosing adenosis." The patient was again seen in June, 1958, approximately one year later, when both breasts became "tender." Examination disclosed diffuse, tender thickening of the upper outer quadrants of both breasts with a suggestion of a mass on the right. MRD-531 was given (1.0 Gm. daily for 2 weeks and then 2.0 Gm. daily for 3 months); the patient complained of moderate nausea and a peculiar tired feeling but other-

wise was able to tolerate the high dosage. When seen on May 11, 1959, she had no complaints and the breasts were much softer. Therapy was continued with a dose of 1.25 Gm. daily. The hemoglobin level, erythrocyte count, white cell count, differential count, nonprotein nitrogen determination, and cephalin flocculation were normal on Jan. 12, 1959, and May 11, 1959.

Patient 16. A 41-year-old white patient was seen in November, 1958, complaining of premenstrual breast tenderness. A left breast resection had been performed in February, 1956, which revealed "chronic cystic mastitis." However, recurrent mastodynia necessitated the use of testosterone and ammonium chloride during most of 1957 and 1958. Examination in November, 1958, revealed diffuse nodularity in the upper outer quadrants of both breasts, and MRD-531 was started in a graduated dose from 250 mg. to 1.0 Gm. daily. Within 6 weeks, marked improvement was noted both subjectively and objectively.

Comment

An estrogen antagonist would seem of value in treating clinical conditions associated with abnormal estrogen metabolism or exaggerated end organ effect. "Chronic cystic mastitis" is thought to be such a process and is often responsible for much patient discomfort. There is some evidence that carcinoma may begin in areas of chronic cystic mastitis, especially where there is intraductal hyperplasia. Surgical removal of the cystic masses is frequently necessary to relieve pain and to eliminate the possibility of malignancy.

A good antagonist must be well tolerated in moderate dosage and be devoid of serious side effects. Further, it should not result in a derangement of normal endocrine function. Steroidal and nonsteroidal substances utilized previously have not met these criteria.

Ethamoxytrithetol (and MRD-531 and MRD-531-A) has been shown in this study to be effective in ameliorating, both subjectively and objectively, many of the undesirable features associated with chronic cystic mastitis. The dose ingested and tolerated is apparently important since, as evidenced in the animal studies,[23, 26] small doses may be estrogenic whereas larger doses are antagonistic to estrogen. The usual starting dose of ethamoxytrithetol used in the present study was 250 mg. orally, once or twice daily for one week, and then a gradual increase each week until a total daily dose of 1.0 to 2.0 Gm. was being taken. In a number of patients, therapy was initiated and continued at a daily dose of 1.5 Gm. from the sixth to the twenty-sixth day of the menstrual cycle. Because of the relatively high incidence of nausea in such patients, the optimum dose regimen seems to be as follows: 250 mg. daily for one week, then an increase of 250 mg. weekly up to a total daily dose of 1.5 Gm. This approximates 25 mg. per kilogram of body weight for an average adult woman.

The optimum duration of the treatment period is undetermined. The shortest treatment period was 4 weeks and the longest was 30 weeks. In most patients no beneficial effects were evidenced before the third week of treatment. Although results were similar if medication was taken for only 20 days of the menstrual cycle, it is simpler to instruct the patient to take the capsules every day. The duration of remission seems unpredictable and unrelated to dosage but is probably correlated with the extent of the disease and the individual patient's own tolerance to discomfort or pain. From the evidence presented, it seems necessary to continue therapy for a minimum period of 3 months, then repeat if mastodynia recurs.

The method and site of action of ethamoxytrithetol is unknown. Unpublished data[26] suggest that it may affect the production or conversion of estrogen intermediary substances or estrogen precursors, or both. Assays of urine have shown a rather considerable rise in the excretion of estradiol following the administration of ethamoxytrithetol, but only if the ovaries are present. Despite the plethora of estradiol in the urine, the end organs may not react to the circulating estrogen. Ethamoxytrithetol may, to oversimplify, alter estrogen metabolism so that while measurable quantities of estrogenic substances are found in the urine, at the cellular level the hormone cannot produce its usual and normal effect.

The subjective improvement noted by 22 of the 25 treated patients was impressive but the results noted by physical examination of the breast were even more striking after several months of continuous treatment. Firm, nodular areas of thickening which were exquisitely tender became softer and more confluent. It should be emphasized, however, that in no patient was a "dominant" lump treated medically instead of by the recognized method of surgical excision. In the diffusely, nodular, and tender breast, however, in which a diagnosis of cystic disease has already been determined, the use of this estrogen antagonist may be of value.

Summary

1. A review is given of the background studies on ethamoxytrithetol.

2. The etiology of "chronic cystic mastitis" is discussed.

3. A study of 25 patients is presented with representative cases.

4. Ethamoxytrithetol is discussed as an estrogen antagonist with consideration of its efficacy, optimum dosage, and possible sites of action.

5. It can be concluded that 22 of 25 patients with chronic cystic mastitis received benefit from this compound and that side reactions are minimal with the sustained release preparation.

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Corticosteroids in the treatment of nonpatent Fallopian tubes

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ATTENTION has been focused in the past decade on the use of corticosteroids in gynecologic problems. The anti-inflammatory, hormonal, and metabolic properties of the drug give it wide therapeutic possibilities. Our investigation is in the realm of its anti-inflammatory effects and was stimulated when Kurzrok[1] reported on 8 patients with cornual occlusion without a previous history of pelvic inflammatory disease, 5 of whom became pregnant.

Since 1952, several articles appeared in the literature concerning the use of corticosteroids and antibiotics in acute pelvic inflammatory disease; Collins[2] reported 7 cases treated successfully. Hurtig,[3] in 1957, presented 45 cases of acute pelvic inflammatory disease; 20 patients were completely cured and, of the 20, 5 became pregnant. He used cortisone, hydrocortisone, prednisone, and prednisolone in heavy dosage. The patients, however, had received specific antibiotic therapy for 2 weeks before the "combined" therapy with cortisone was instituted.

Wills,[4] in 1956 and again in 1958, reported 22 cases of acute pelvic inflammatory disease; 17 patients were cured and 3 of the 17 became pregnant. In 1956, Bret[5] injected a mixture of 25 mg. of hydrocortisone with streptomycin alone or combined with penicillin into the Fallopian tube. The method of injection is similar to instilling a dye to obtain a hysterogram. The treatment is repeated two to three times weekly, depending on the results obtained. Bret did not report his results.

Houghton,[6] in 1954, successfully treated active pulmonary tuberculosis using combined corticotropin and chemotherapy. He showed not only that it was safe but that corticotropin prevented allergic reactions to chemotherapy in sensitive individuals. As a result of experiments with guinea pigs he suggested that cortisone may be used safely in combination with chemotherapy. These findings suggest further investigation in the use of the steroids in pelvic tuberculosis, especially in the latent type associated with nonpatent salpinges.

Rationale for corticosteroid therapy

Observations in the rabbit and monkey by Westman[7] indicate that the fimbriae of the tube expand over the ovary at the time of ovulation in such a manner that the lateral surfaces of the ovary present themselves to the tube.[8] These findings have been partially confirmed in the human by Doyle,[9] who has observed, by means of the culdoscope, that the migration of the ovum from the ovary into the tube is facilitated by flotation and siphonage.[9] It may be concluded from these and similar studies that a normal mucosa and musculature are essential for the proper passage of the ovum through the Fallopian tube. Therapy of nonpatent tubes, therefore,

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Fig. 1. Case 1, bilateral closure of Fallopian tubes at fimbriated ends (February, 1954).

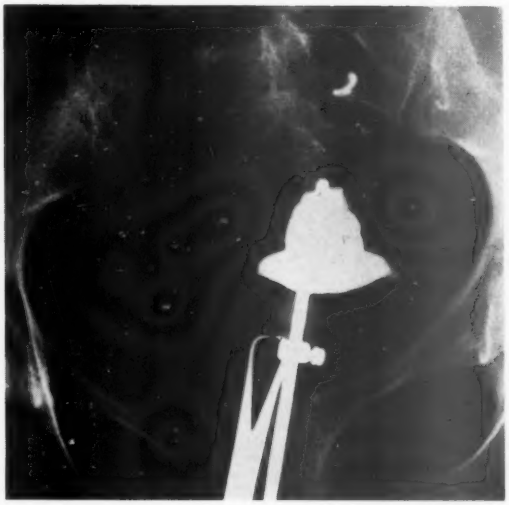


Fig. 2. Case 1, visualization of left tube following corticosteroid therapy (October, 1956).

must be directed toward both correction and improvement of physiologic function. A recent analysis[10] of tuboplastic operations indicates that the best results were obtained by salpingolysis, the most often employed procedure, while resection anastomoses or fimbrioplasty produced the poorest results. Salpingolysis, however, corrects only the peritubal pathology.

Ectopic gestation has become more frequent since the use of antibiotics for pelvic inflammatory disease,[11] indicating only partial healing of the tubal mucosa. In the cases presented in this study, intensive antibiotic therapy was ineffective in producing either partial or complete healing of the tubes. Corticosteroids appear, therefore, to have corrected residuals of previous pelvic inflammatory disease where antibiotics have proved ineffective. It also appears that the physiologic action of the Fallopian tube is improved by correcting the defects of previous inflammation within the tube.

Ovarian function, as indicated in basal temperature readings, was also improved by corticosteroid therapy, suggesting its hormonal effect.

Material and methods

To date 20 consecutive cases were studied. Fifteen of these were from the Infertility Clinic of Cumberland Hospital where the incidence of pelvic inflammatory disease is high and the remaining 5 were from private practice. All patients treated were those showing repeated evidence of fimbrial occlusion except one case of cornual occlusion. Eighteen cases had received antibiotic therapy for the acute or subacute phase and were in a healed stage with normal white blood cell counts and sedimentation rates, the remaining 2 denied having had previous therapy.

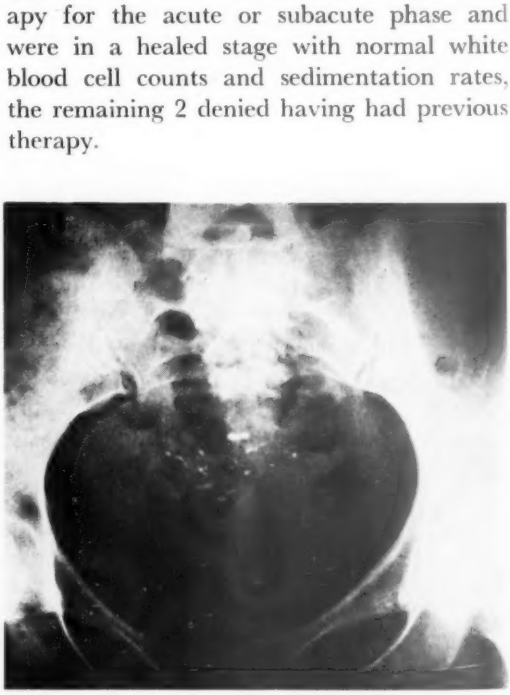


Fig. 3. Case 1, patency of left tube following corticosteroid therapy (October, 1956).



Fig. 4. Case 3, bilateral closure of Fallopian tubes at cornual ends (April, 1954).



Fig. 6. Case 3, patency evident (January, 1957).

We administered only corticosteroids, since antibiotic therapy combined with steroids has proved successful in a number of patients with pelvic inflammatory disease and it seemed important to evaluate only one factor in treatment.

Before instituting therapy we attempted to obtain at least two sets of x-ray studies either months or years apart, which seemed to eliminate the question of hysterosalpingography by itself acting as a therapeutic agent.



Fig. 5. Case 3, tube normal (January, 1957).

Results

Of these 20 patients, tubal patency was achieved in 11, 6 of whom conceived. Two have been delivered of normal infants, 2 are near term and the other 2 are in the early months of gestation (Case 1 is of a patient now in the fourth month of gestation after aborting the first pregnancy following therapy). Two patients are still undergoing therapy and have been under treatment less than 3 months. Seven represent failures and it is interesting to note that two of these had resection anastomoses of the tubes with polyethylene tubing 18 months prior to corticosteroid therapy.

Corticosteroid therapy is given initially for a period of 3 months and may be continued or repeated after a one-month interval. The early patients received cortisone acetate,* 50 mg. daily by tablet and 50 mg. intramuscularly twice weekly. The remaining patients received prednisolone acetate,† 10 mg. daily by tablet and 25 mg. intramuscularly twice weekly. Uterotubal insufflation with gas or dye was held in abeyance during the initial course of treatment.

All patients were placed on a salt-free

*Cortogen, Schering Corporation, Bloomfield, New Jersey.

†Meticortelone acetate, Schering Corporation, Bloomfield, New Jersey.

Table I. Summary of 11 cases of nonpatent tubes treated successfully

Case	*Age*	*Involuntary sterility*	*Previous history*	*Previous therapy*	*Nonpatency demonstrated by*	*Present therapy*	*Response to therapy*
1	27	5 years	PID in 1950, 1951, 1952	Antibiotics in 1950, 1951, 1952, 1956	Salpingogram, February, 1954, and July, 1956	Cortogen,* 6 months	Patency revealed by x-ray, October, 1956; April, 1959, aborted third month; December, 1959, fourth month gestation
2	28	2 years	PID in 1947	Penicillin therapy in 1947	Salpingogram, April, 1954, April, 1956	Cortogen, 3 months	Patency revealed by x-ray, September, 1956; repeated Rubin tests, November, 1956, March, 1957
3	25	4 years	Noncontributory (only case of cornual occlusion)	None	Salpingogram, April, 1954, July, 1956	Cortogen, 5 months Meticortelone†, 3 months	Patency revealed by x-ray, January, 1957; full-term delivery, March, 1958
4	34	9 years	Right salpingo-oophorectomy for tubovarian abscess, July, 1955, lysis of adhesions	Antibiotics—September through October, 1955	Salpingogram, December, 1955, December, 1956	Cortogen, 5 months	Patency revealed by x-ray, March, 1957
5	32	5 years	Postabortal infection, 1950	Antibiotics—repeated courses 1950 through 1956	Salpingogram, January, 1956, September, 1956	Cortogen, 3 months	Patency revealed by x-ray, March, 1957
6	32	5 years	Bilateral salpingostomy, August, 1955, (elsewhere)	Dihydrostreptomycin postoperative—August to October, 1955	Rubin tests, January, February, 1956; salpingogram, March, 1956	Meticortelone, 3 months	Patency, revealed by x-ray, September, 1957
7	25	6 years	PID in 1955, 1956	Antibiotics—1955, 1956	Rubin test, salpingogram, March, 1956, July, 1957	Meticortelone, 3 months	Patency revealed by x-ray, November, 1957; fourth month gestation
8	34	2½ years	Noncontributory	None	Salpingogram, June, 1957; repeated Rubin tests, July, August, September, 1957	Meticortelone, 3 months	Patency revealed by x-ray, February, 1958
9	27	5 years	Oophorectomy and appendectomy, 1949; postabortal infection, 1951	Antibiotics—1951	Culdoscopy and insertion of indigo carmine	Meticortelone, 3 months	Pregnancy, full-term delivery, May, 1958

Table I—Cont'd

Case	*Age*	*Involuntary sterility*	*Previous history*	*Previous therapy*	*Nonpatency demonstrated by*	*Present therapy*	*Response to therapy*
10	33	6 years	Fibroids, PID, clubbed tubes	Myomectomy, lysis of tubal adhesions fimbrioplasty March, 1958 (elsewhere)	Postoperative salpingogram revealed clubbed tubes, February, 1959	Meticortelone, 3 months	Late pregnancy
11	32	11 years	PID in 1950, 1952, 1953	Antibiotics—1950, 1952, 1953	Salpingogram, June, 1954, April, 1959; culpotomy, insertion of indigo carmine, April, 1959	Meticortelone, 3 months	Early pregnancy

*Cortogen, 50 mg. daily by tablet, 50 mg. intramuscularly twice weekly.

†Meticortelone acetate, 10 mg. daily by tablet, 25 mg. intramuscularly twice weekly.

diet with limitation of fluids. They were further advised to report between visits the development of any toxic symptoms, including headaches, lassitude, weakness, abdominal pain, and swelling of the legs. We observed our patients routinely for excessive weight gain and edema of face, breasts, or legs.

None of the 20 patients developed toxic symptoms during the first 3 months of treatment. Five of the 20 required a second course of therapy. Only 2 of the 5 developed evidence of edema, one with marked engorgement of the breasts, the other with a "moon facies." In both cases the symptoms disappeared soon after the withdrawal of the drug. Table I summarizes the 11 cases and the response to therapy.

The age range of the total 20 patients was from 25 to 34 years. In the patency group 7 were nulliparas and 4 were multiparas; only 2 of the latter had had previous full-term deliveries. In the failure group 4 patients were nulliparas and 3 were multiparas; only one of the latter had had a previous full-term delivery. In the pregnancy group 3 were nulliparas and 3 were multiparas, 2 of whom had had previous full-term deliveries. Figs. 1 to 9 represent a sampling of the x-ray films obtained in the 11 cases.

Comment

In dealing with a drug possessing such wide biologic effects, emphasis should be placed on the dosage, mode of administration, and a complete understanding of all possible reactions. Cortisone and hydrocortisone had to be used in high dosage in order to obtain full therapeutic effects. In our early cases, Cortogen (hydrocortisone) was used since it was the only drug available at the time. The addition of a second double



Fig. 7. Case 8, bilateral closure of the tubes at the fimbriated ends (June, 1957).



Fig. 8. Case 8, tubes normal (February, 1958).



Fig. 9. Case 8, dye present in peritoneal cavity indicating patency (February, 1958).

bond in the A ring of hydrocortisone resulted in Meticortelone acetate, a steroid of greatly increased potency with significantly less undesirable effects on electrolyte and water metabolism. With this improved steroid the dose was reduced to 10 mg. daily by mouth and 25 mg. intramuscularly twice weekly in contradistinction to the high doses used by Collins,[2] Hurtig,[3] and Wills.[4]

While our dosage schedule appears to be within a safe range, certain precautionary measures must always be borne in mind when this potent hormone is administered. Constant improvement of the original drug is being made in order to reduce the unwanted side effects of sodium retention, edema, hypertension, peptic ulcer, and osteoporosis. Even in therapeutic doses the glucocorticoids can inhibit the corticotropin (ACTH) production by the pituitary and thereby depress the function of the adrenals temporarily.

The unwanted side reactions which developed in 2 of our patients appeared near the completion of the second course of therapy. It is interesting to note that an interval of over 3 months elapsed before the second course was instituted. Whether or not this interval had any significance in building up an intolerance to the drug will be determined only by further clinical studies.

Summary

1. Twenty cases of tubal occlusion proved by repeated radiologic examinations, Rubin test, and/or culdoscopy were treated with corticosteroids.

2. Eleven of the 20 cases demonstrated tubal patency after 3 to 6 months of treatment. Of the 11 patients, 6 became pregnant. Two were delivered of normal infants at term; 2 are in the early and 2 are in the later months of gestation.

3. By constant refinement of cortisone and hydrocortisone newer products are becoming available. The dose and duration of therapy can therefore be reduced, giving the clinician a greater safety factor. The avoidance of the unwanted deleterious side reactions widens the scope of this potent hormone in gynecologic problems.

The Meticortelone acetate and Cortogen used in these studies were supplied through the courtesy of the Schering Corporation, Bloomfield, New Jersey.

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Pelvic abscess

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THE problem of pelvic abscess in the female continues to be important to gynecologists and general surgeons. In 1949, Abbott[1] stated, "The incidence of pelvic abscess has decreased remarkably." The records of the Victoria General Hospital in Halifax show no such decrease and we continue to see a fairly uniform incidence from year to year. Despite the liberal use of potent antimicrobial agents to treat pelvic infection, abscess continues to be the end result of many of these cases.

Over the years, the management of these abscesses has generally been surgical. The ruptured tuboovarian abscess was studied by Vermeeren and TeLinde,[2] who collected 400 cases. They pointed to a 90 per cent mortality rate with delayed operations and only 12 per cent following immediate transperitoneal drainage. Ordinarily, unruptured pyosalpinx is treated conservatively, but many of these women ultimately come to operation because of recurrence, pain, or continuing ill health. The traditional teaching with regard to abscess in the pouch of Douglas has been to open through the posterior fornix when fluctuation is established and drain by means of a T tube for several days.

The experience at our hospital prior to 1949, in common with many other centers, was all too often a tiresome sequence of complications following these traditional methods. In 1957, Schreier, Adams, and Everett[3] reported from Memphis an experience with 309 cases of pelvic abscess—168 of their cases were treated by initial colpotomy, i.e., those cases approachable from the midline. They stated, "Even though a high percentage require additional surgical treatment later, colpotomy and antibiotics may eliminate the necessity for pelvic laparotomy." The balance of their patients were treated by primary definitive operations, either immediate or delayed, and in their series there were no subsequent pregnancies.

In 1952, Tupper[4] from this center published a preliminary report on 14 cases of pelvic abscess treated by a new method. In this report he described the difficulties with previous methods as follows: "(1) The insertion of a T-tube into a small opening in the pouch of Douglas was difficult and there was always danger to the bowel in making the incision. (2) There often remained a draining sinus that could cause a profuse discharge. This was associated with bouts of fever, chills, and general malaise from absorption when it did not drain well. This state of things could only be cured by removal of the pus sac, which meant removal of the pelvic organs—a formidable operation. (3) The hospital stay was long—often lengthening into months."

The new method is simply to drain any abscesses accessible from below (whether in the cul-de-sac or the tuboovarian region) by means of a large bore (No. 16 or larger) needle and then instil penicillin and streptomycin in the abscess cavity. Usually, 1 million units of penicillin and 1 Gm. of streptomycin are used in 10 ml. of saline. Aspiration is repeated as often as the cavity refills. Only rarely is any additional therapy

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(other than bed rest and the systemic administration of the appropriate antimicrobial agent) required.

This paper describes the result of 10 years' experience with this method of management of pelvic abscess at the Victoria General Hospital in Halifax. All patients with pelvic abscess on the Dalhousie University service were treated in this way, and in addition several private patients treated similarly by our own staff members are included.

In all, 71 patients were treated. We were able to obtain satisfactory follow-up in 49 cases (Table I). This was accomplished through examination in our own clinic and by correspondence with family doctors, other hospitals, or the patient herself. Despite our efforts we could not locate 22 patients.

The information obtained from our study of these cases is given in Tables II-V.

Tables II to V give the basic clinical information obtained at examination. As one would expect, pelvic abscess occurred predominantly in the 20 to 40 age group. The usual disturbances of temperature, pulse, and leukocyte count were found, but anemia was not a characteristic finding. Most of the group showed some evidence of toxicity from infection and almost all had abdominal tenderness, although surprisingly few showed evidence of general peritonitis. Abscesses were located most commonly in the midline, but were also found together or separately on one or other side. The etiology of these abscesses varied considerably, and we were surprised to find 7 postoperative cases and 2 occurring after radium application for carcinoma of the cervix. In neither of these cases did the operator feel he had perforated the uterus, nor did fistulas develop.

Streptococcus hemolyticus, usually anaerobic or microaerophilic, was the most common organism cultured and indeed was the rule in the postabortal and postpartum cases. Twenty cases with frank pus showed no growth on culture (Table VI).

Most cases subsided with one or two aspirations, but in one case aspiration was

Table I. Follow-up

No. years	*No. patients*
10	3
9	0
8	4
7	1
6	3
5	2
4	8
3	8
2	5
1	5
Less than 1	10
Not known	22

Table II. Age

Less than 20	3
20-29	35
30-39	21
40-49	9
More than 50	3
Total	71

Table III. Basic measurements

Peak temperature	
Normal-100° F.	11
100-102° F.	37
Over 102° F.	28
Pulse	
Less than 90	6
90-110	28
More than 110	37
White blood count	
Less than 10,000	12
10,000-20,000	42
More than 20,000	12
Hemoglobin (Gm. per cent)	
Less than 9	4
9-12	27
More than 12	34

Table IV. Clinical findings

Toxic	53
Tenderness	70
Rigidity	18
General peritonitis	13
Ileus	4

Table V. Site of abscess

Right	19
Left	24
Midline	53

Table VI

Etiology	
Pelvic inflammatory disease	29
Tuberculosis	2
Postabortal	11
Postpartum	4
Postradiation (cancer of cervix)	2
Postoperative	7
Appendicitis	1
Not specified	15
Organism cultured	
Streptococcus	25
Escherichia coli	12
Aerobacter aerogenes	6
Micrococcus	5
Enterococcus	5
Proteus	3
Bacteroides	1
Clostridium welchii	1
Bacillus subtilis	1
Staphylococcus	1
Diphtheroids	1
Mycobacterium tuberculosis	2
No growth	20
No report	9

Table VII

Aspirations	
1	34
2	29
3	3
4	3
5	1
6	0
7	1
Amount aspirated	
1-50 ml.	61
50-100 ml.	30
Over 100 ml.	45

done seven times. The amount of pus aspirated varied from a few milliliters to 400 ml. In all cases, frank pus was obtained (Table VII).

Additional local therapy was rarely used (Table VIII), but in 3 cases incision and drainage was carried out early in the study for reasons not apparent in 2 cases, and in one case because the abscess pointed in the flank.

One of the great advantages of this method of treatment appears to be the definite shortening of hospital stay (Table IX). Most of the patients were in the hospital only once but a few required two or more admittances. Regardless of the number of admittances, the total number of days of hospital treatment averaged only 17.9—considerably less than the "weeks or months" described in many reports. After aspiration and the injection of the antibiotics the response of the patient is often dramatic and usually gratifying. There may be a temporary rise in temperature for a few hours, but this usually subsides within the day to normal. If the abscess refills the temperature and pulse will gradually rise. After the last aspiration, the average number of hospital days was 9.6.

Although the convenience, safety, and efficiency of this method of treatment has been most gratifying to those of us who have

Table VIII. Additional therapy

Hot douches	9
Incision and drainage	3
Diathermy	6

used it, it is the results obtained which have naturally concerned us most (Table X).

Most gratifying has been the fact that of 49 patients followed, there were 8 who became pregnant. All but one carried to term and one woman had had 2 pregnancies at the time of follow up. Most authorities have written that pelvic abscess practically eliminates any possibility of future pregnancy. We have reason to be more optimistic.

Table IX

Total hospital days	
Maximum	68
Minimum	5
Average	17.9
Days after aspiration	
Maximum	47
Minimum	1
Average	9.6
No. of admissions	
1	56
2	11
3	1
4	3

Table X. Results

Pregnancy	
Of 49 patients followed, 8 women had 9 pregnancies (8 full term; 1 abortion)	
Further treatment	
Operation (usually hysterectomy and salpingo-oophorectomy), 12 cases	
Of these, 7 had symptoms and 6 had obvious pelvic disease, all well at follow-up	
Patients not operated on	
37 followed up	
Only 2 had any symptoms of ill health and no pelvic disease noted	

Twelve patients are known to have had further operations, roughly 25 per cent of those followed. This is a lower proportion than usually quoted. Of these, only 7 had symptoms preoperatively and 6 (50 per cent) had obvious pelvic disease at operation. All were well at follow up. Of the 37 patients followed up and having no further treatment, only 2 had symptoms of ill health and neither had evidence of pelvic disease.

Comment

Why has this method of dealing with pelvic abscess been successful? The same method has been tried and abandoned for the treatment of abscess elsewhere in the body. It contravenes the established surgical principle of open drainage of pus. It is doubtful if the injected antibiotic will really permeate through the thick inflammatory barrier of the abscess wall in significant amounts, nor will the systemic antibiotic be likely to do more than control bacteremia and the organisms at the vascular periphery. Perhaps the effect of posture and gravity aid in the collapse of the cavity, but, in any case, we have now had enough experience to know the method is effective. Much has been written of the danger due to fulminating peritonitis from rupture in cases of tuboovarian abscess, localization in the ovary or broad ligament.[5] However, we have treated these lateral localizations in the same way with uniformly gratifying results without complications, and with one exception no cases were drained abdominally. The technical difficulty and hazard in patients coming to operation has been reduced considerably and the large majority of patients have not required any further operation.

Summary

We have reviewed our experience with 71 cases of pelvic abscess treated over a 10 year period, 1948 to 1958, at the Victoria General Hospital in Halifax. Treatment consisting principally of needle aspiration and the injection of antibiotics has been associated with a greatly reduced hospital stay. There were complete cures in 75 per cent of the 49 patients with follow-up.

Of the total number of patients treated 8 are known to have had subsequent pregnancies.

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Manson's schistosomiasis of the Fallopian tube

A case report

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INFESTATION of the Fallopian tube with *Schistosoma mansoni* occurs infrequently. Arean[1] found 18 gynecologic lesions due to *Schistosoma mansoni* among the 78,238 surgical specimens from 1925 through 1955 at the University of Puerto Rico. The Fallopian tubes were affected in 5 instances. Armbrust[2] in his extensive review on schistosomiasis of the genitourinary tract reported one instance of tubal disease. The paucity of reports on this complication in the world literature has prompted the following presentation.

J. P., a 30-year-old gravida vii, para vii, Puerto Rican woman, was admitted to the Gynecology Service of the New York Medical College–Metropolitan Hospital Center on Jan. 15, 1959, for surgical correction of a cystocele-rectocele and uterine descensus with severe stress incontinence of urine. The patient's past history was not remarkable. She had had 7 uneventful full-term deliveries between 1949 and 1958, all in New York City, and she stated that she did not go back to Puerto Rico during this period of time.

On Jan. 21, 1959, a vaginal hysterectomy, unilateral salpingo-oophorectomy, and colpoperineorrhaphy were performed. The postoperative course was uneventful, and the patient was discharged on the tenth hospital day in good condition.

Pathology report. The gross and microscopic findings in the uterus and cervix were unremarkable. The tube was 7 cm. long and 0.8 cm. in its largest diameter. The serosa was smooth and glistening; the lumen was patent. Microscopic examination revealed numerous pseudotubercles in the stroma of the mucosal folds. The tubercles were composed of giant and epithelioid cells surrounded by a zone of fibroplastic proliferation with round cell infiltration. Many of the giant cells contained the typical necrotic shells of the ova of *S. mansoni* with characteristic lateral spine.

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Comment

Of the 3 known species of the parasitic worm Schistosoma (blood flukes) only *S. mansoni* is encountered in the Western Hemi-



Fig. 1. Pseudotubercle in the tubal mucosa. Giant cell containing egg of *S. mansoni* is surrounded by epithelioid cells and fibrous connective tissue matter.

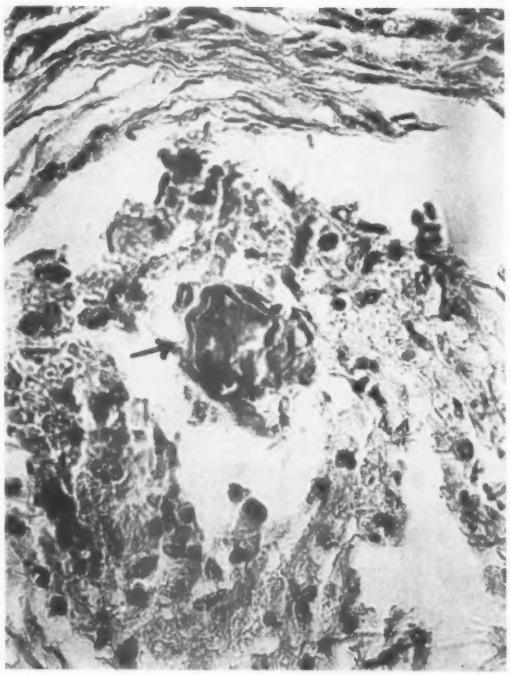


Fig. 2. High power view, showing the "crumpled" appearance of the *S. mansoni* egg shell with the characteristic spine.

sphere; *S. japonicum* being endemic in the Far East and *S. haematobium* in Africa. *S. mansoni* infestation is prevalent among Central and South American population. The incidence in Puerto Rico was found to be 28 per cent by stool examination and 14.6 per cent by autopsy material. The contagion occurs by eggs passed with feces. The eggs hatch in fresh water and miracidia enter the intermediary host, a snail. Free swimming cerceriae leave the snail and penetrate the skin and mucous membranes of humans, producing a local skin reaction, so-called "swimmer's itch." The worms mature and copulate in the veins of general circulation and lay eggs in the small radicles of the portal system. The eggs of *S. mansoni* are rarely found in the genital tract, which is outside the portal territory, and their occasional presence is explained by migration through anastomotic channels. The transmission of the disease into humans is impossible without the intermediary host and no known species of North American snail acts as the vector. There are, therefore, no known cases of *S. mansoni* being contracted in the United States.

The ova of the parasite stimulate chronic granulomatous reaction of the surrounding tissue which becomes a source of clinical manifestations. It produces gastrointestinal disturbances and finally cirrhosis of the liver.

The patient presented here must have contracted the disease before she left Puerto Rico permanently, or at least 10 years prior to the operation. She apparently continued to discharge ova but remained remarkably symptom free. The involvement of the Fallopian tube by the granuloma did not interfere with this patient's fertility as attested by the fact of her 7 full-term deliveries subsequent to infestation.

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Enterobius vermicularis granuloma of pelvis

A case report

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GRANULOMATOUS lesions caused by the presence of *Enterobius vermicularis* and its ova are rare. In 1950, Symmers[1] reviewed the literature and found 16 cases of pelvic lesions due to *Enterobius vermicularis* of which only 5 were symptomatic. He added 2 nonsymptomatic cases of his own. In 1954, Nairn and Duguid[2] and, in 1956, Shenken and Tamisiea[3] added 2 more symptomatic cases. In 1958, Arthur and Tomlinson[4] reported a case with nonsymptomatic granulomas of the pelvic region.

Mrs. E. M., a 47-year-old gravida xv, para xiv, entered the hospital complaining of severe right flank pain of about 15 hours' duration. The patient had noted the onset of this pain 2 months previously, at which time it consisted of mild right flank and low back pain with associated fever, anorexia, nausea, and occasional vomiting; this continued for a period of 10 days. There was a recurrence of this illness for several days one month prior to the present attack.

The past history was noncontributory. She had 12 living children, the youngest aged 3 years. There was a history of a pregnancy terminating as a hydatidiform mole 7 years previously. She had noted an irregular mass in her neck for 14 years.

The significant physical findings were confined to the pelvis and the thyroid. There was multinodular enlargement of the thyroid, more marked in the right lobe. There were no signs of toxicity. There was chronic cervicitis and moderate hypertrophy of the cervix. The body of the uterus was very firm and fixed to a hard mass occupying the right adnexal region. This indurated, nontender mass was 6 to 8 cm. in diameter and was fixed to the right lateral and posterior pelvic walls. The left adnexal region was normal to palpation.

Laboratory investigation revealed a hemoglobin level of 13.2 Gm. per cent and a white blood count of 7,700 with a normal differential. Serologic tests for syphilis were negative. Routine urinalysis and urine culture were negative. *Ascaris lumbricoides* ova were present in the stool. An intravenous pyelogram revealed prompt excretion through both kidneys but there was a definite dilatation of the right renal pelvis and upper ureter which appeared to be due to obstruction of the pelvic portion of the right ureter. There was an extrinsic mass indenting the right side of the urinary bladder.

The patient was operated upon with the preoperative diagnosis of right adnexal mass due to degenerating intraligamentous fibroid or tumor of the right ovary. The operative findings were those of a unilateral tuboovarian mass with right hydrosalpinx and a unilocular cystic enlargement of the right ovary, both adherent in a dense fibrous mass to the right lateral and posterior walls of the pelvis, the right lateral and posterior surfaces of the uterus, and the tip of the appendix vermiformis. There were no other peritoneal or omental adhesions. The left Fallopian tube and ovary were grossly normal. A total hysterectomy, bilateral salpingectomy, right oophorectomy, and appendectomy were performed.

The postoperative course was complicated by a deep abdominal wound infection due to *Esch-*

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erichia coli and a purulent drainage from the open vaginal vault due to *E. coli* and a member of the paracolon group of bacteria.

Three months postoperatively the patient complained of a nonspecific vaginal discharge but was otherwise well. A repeat intravenous pyelogram at this time revealed no evidence of dilatation of the right ureter or calyceal system and no evidence of pressure on the bladder.

Histologic study of the ovarian cystic lesion revealed dense infiltrates of lymphocytes and plasma cells in the lining with extension into the dense fibrous stroma beneath. The right Fallopian tube had villi fused forming pseudo-glands. In the tunica propria and among the muscle coats were dense infiltrates of lymphocytes and plasma cells. There were no ova or granulomas. The appendix vermiformis had a mucosa with a lymphoid stroma containing glands lined by columnar epithelium. There were no significant changes in the submucosa or muscle coats. In the serosa was a segment of an adult female *Enterobius vermicularis* (Fig. 1), surrounded by a basophilic amorphous material and granulomatous tissue composed of epithelioid cells with scattered lymphocytes. The characteristic ova were clearly seen within the worm (Fig. 2). There were no ova in the surrounding tissues. There were no significant pathological findings in the left Fallopian tube, in the endometrium or myometrium, or in the cervix.

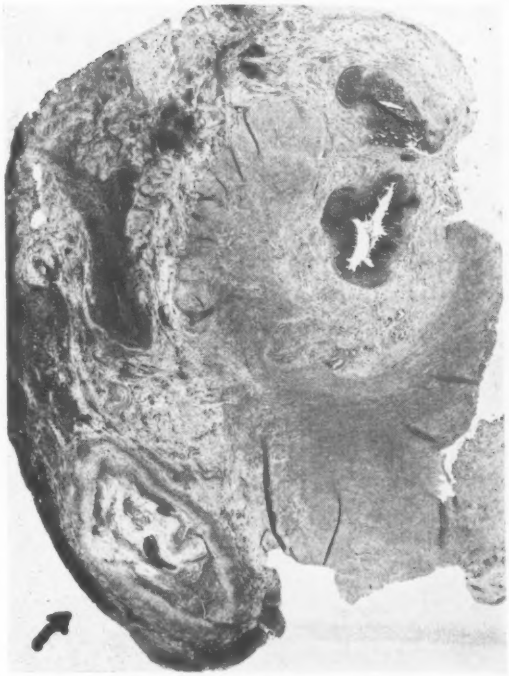


Fig. 1. Photograph of adult female *Enterobius vermicularis* in serosa of appendix vermiformis.

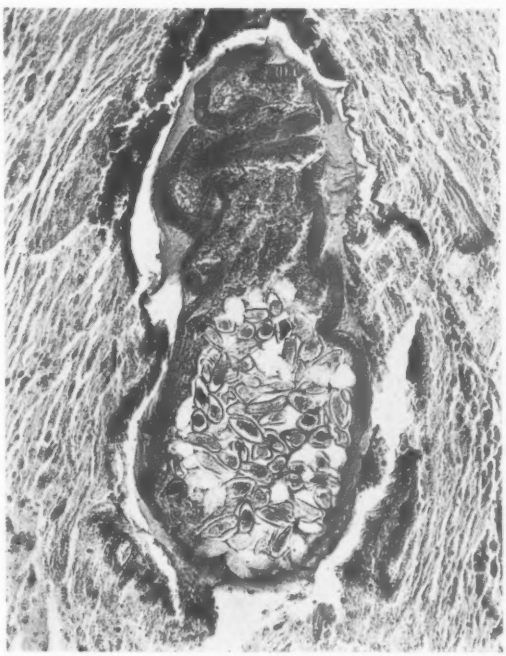


Fig. 2. *Enterobius vermicularis* ova within the adult worm.

Comment

The evidence of granulomas due to *Enterobius vermicularis* in endometrium, myometrium, Fallopian tubes, and peritoneum and the logic which have been clearly presented by Symmers[1] and Shenken and Tamisiea[3] seem to point conclusively to migration of the female enterobius from the anal region through the female genital tract to the peritoneal cavity. The absence of any evidence of involvement of the mucosa or muscularis of the appendix or other intestinal lesions, but the marked gross and microscopic evidence of unilateral salpingo-oophoritis in this case, support this theory. Although thorough investigation postoperatively failed to reveal the presence of enterobiasis, there was a history of pruritus ani, and *Ascaris lumbricoides* were present. The rather severe presenting symptoms were in part due to right

ureteral obstruction and dilatation which resulted from the pressure of the granulomatous tuboovarian mass upon the pelvic portion of the right ureter.

Conclusion

An additional case of *Enterobius vermicularis* granuloma of the female genital tract and pelvic peritoneum is reported, and all evidence in the case supports the thesis that the female enterobius migrated from the anal canal up through the genital tract to a point of lodgement in the serosa of the appendix vermiformis.

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Adenoacanthoma of the endometrium

A report of 24 cases and a review of squamous metaplasia

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ALTHOUGH the term "adenoacanthoma of the endometrium" is mentioned fairly often in the gynecologic literature, specific studies of this uncommon lesion are rare. Impressions garnered solely from sporadic case reports have sometimes been perpetuated by subsequent authors, and there are few reports of collected and properly analyzed cases. It is perhaps for this reason that diametric opinions exist on several aspects of this lesion. There is not only variance of opinion regarding the origin of the squamous component but also disagreement concerning the potential of an adenoacanthoma for local invasion and distant metastases. Certain authors therefore state that the presence of squamous cells in an endometrial adenocarcinoma indicates a poorer prognosis than for the ordinary adenocarcinoma, while others insist that the prognosis is improved by the presence of squamous metaplasia. It is both surprising and regrettable that a divergence of opinion of this magnitude appears to exist and that our documented knowledge of this malignant lesion is limited.

This study is based upon a series of 24 adenoacanthomas treated between 1930 and 1959 and was undertaken to determine if the presence of squamous metaplasia implies a lesion more benign or more malignant than the ordinary endometrial carcinoma, in terms of histologic pattern, myometrial invasion, spread beyond the corpus, and over-all prognosis. The subjects of experimental squamous metaplasia of the endometrium and of squamous metaplasia associated with benign endometrial conditions are fundamental to this subject and therefore worthy of review.

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Experimental squamous metaplasia

Squamous metaplasia has been produced experimentally in the endometrium and other organs of various animals by different methods, all of which consist of inflicting some type of injury upon the normal epithelium.

D'Erchia,[7] in 1900, produced squamous metaplasia in guinea pigs by ligation of one uterine horn and removal of the fetus, causing a retention of products of conception for 2 months. Momigliano,[46] in an interesting experiment suggested by an unusual case history, was able to produce squamous metaplasia in the endometrium of a rat by prolonged trauma with a foreign body.

Wolbach and Howe[69] demonstrated extensive keratinization of the uterine cavity of rats maintained on a diet deficient in vitamin A. A number of investigators[12, 15, 16, 30, 31, 37, 38, 60, 71] have adequately documented the injurious role of the prolonged administration of estrogen in producing squamous metaplasia of the uterine epithelium in mice, guinea pigs, and rats (Figs. 1 and 2). Bo[3, 4] recently studied the relationship of vitamin A deficiency and estrogen in causing metaplasia and stated that, while the mode of action of vitamin A in main-

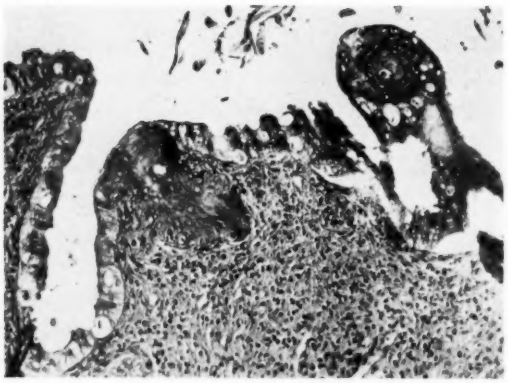


Fig. 1. Squamous metaplasia occurring on the surface of the rat endometrium as the result of prolonged estrogen administration. (Hematoxylin and eosin. ×130; reduced ⅓.) (Courtesy of Dr. C. F. Fluhmann.)

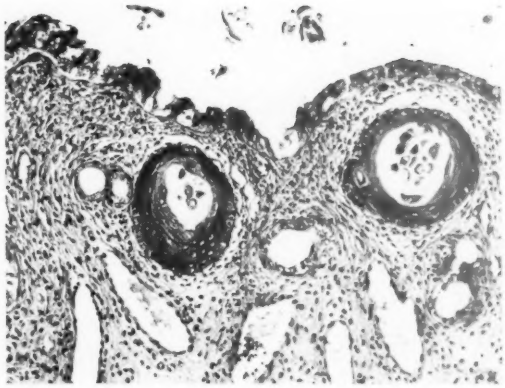


Fig. 2. Squamous metaplasia occurring within the endometrial glands of the rat following prolonged administration of estrogen. (Hematoxylin and eosin. ×130; reduced ⅓.) (Courtesy of Dr. C. F. Fluhmann.)

taining normal uterine epithelium is unknown, disruption of a balance between estrogen and vitamin A apparently may lead to squamous metaplasia.

Lipschütz[34] produced extensive squamous metaplasia of the endometrium in the Cebus monkey by prolonged administration of estrogen, but such changes have not been duplicated in the Rhesus monkey, suggesting a species difference in sensitivity of the endometrium to the effects of estrogen. It should be noted that squamous metaplasia of the endometrium has also been produced in experimental animals by the prolonged administration of chorionic gonadotropin[13] and of androgens[30]; the metaplastic change is therefore not a specific effect of estrogen.

Squamous metaplasia has also been produced in other organs of experimental animals by various forms of trauma. The metaplastic change has been observed in the bladder of rabbits as a result of inflammation,[35] in the trachea of dogs and rabbits following inflicted wounds in that organ,[28] in the lungs of rats after induced bronchopneumonia,[64] and in the breasts of rabbits following injection of scharlach R.[11]

It is not within the realm of this discussion to expand on these studies of squamous metaplasia in experimental animals, nor is it entirely proper to apply observations in lower species directly to similar changes in the human. These studies are nevertheless fundamental since the changes described are very similar to those in the human and contribute to our understanding of squamous metaplasia occurring in the human endometrium.

Squamous metaplasia associated with benign conditions

Squamous metaplasia may be encountered in many nonmalignant conditions of the endometrium, which is only one of many areas in which the lesion may be noted in the human. Squamous metaplasia has been described in the larynx, trachea, bronchus, thyroid, esophagus, stomach, intestines, gall bladder, pancreatic ducts, kidneys, bladder, prostate, Fallopian tube, meninges, and anterior lobe of the pituitary gland.

Zeller,[70] in 1885, applied the term "icthyosis uteri" to cases in which squamous metaplasia resulted from the intrauterine application of caustics such as formalin or iodine. Mainzer[39] noted similar changes in the uterine epithelium after formalin vaporizations. Other nonmalignant conditions in which squamous metaplasia may be noted include endometrial hyperplasia,[15] endometrial polyp[15] (Fig. 3), senile endometrium,[15] tuberculous endometritis,[1, 15] puerperal endometritis,[15] pyometra,[5, 19] and chronic inversion of the uterus.[55] Squamous metaplasia

has also been reported during regeneration of the uterine mucosa after curettage[66] and as a possible sequel to intrauterine radium.[47]

Especially interesting are the earlier studies which reported the finding of stratified squamous epithelium in the endometrium of newborn and older infants. Meyer[43] reported areas of 4 to 8 rows of stratified squamous cells in the endometrium of the newborn. Friedlaender[17] reported similar changes in infants, and Wilson and Dubois[68] recorded several cases in infants with known vitamin A deficiency. Natanson[49] reviewed a group of cases and concluded that squamous epithelium occurred in the endometrium of 10 per cent of children up to the age of 2½ years with subsequent disappearance of the squamous cells as the uterus developed.

Although squamous cells are not usually found in the normal endometrium, it is thus apparent that they may occur in a wide variety of benign uterine conditions. The squamous cells are usually mature, well-differentiated cells without malignant characteristics, and their presence should not be interpreted as implying a more serious lesion.

Squamous metaplasia associated with endometrial carcinoma (adenoacanthoma)

Since Herxheimer's description[24] of the tumor in 1907, sporadic reports have appeared labeling it "adenoacanthoma of the uterus," "adenocancroid of the uterus," or "adenocarcinoma of the endometrium with squamous metaplasia." However, many of these cases, after more critical examination, are found to represent either endometrial hyperplasia with concomitant acanthosis or adenocarcinoma where degenerative changes in the glandular cells have produced cells which simulate squamous cells (Fig. 4).

The term "adenoacanthoma of the endometrium" should also not apply to the following entities: (1) squamous cell carcinoma of the corpus secondary to a cervical carcinoma, (2) squamous cell carcinoma of the cervix coexistent with an endometrial carcinoma, (3) the rare primary squamous cell carcinoma of the corpus, (4) endometrial carcinoma which shows squamous metaplasia in adjacent hyperplastic areas but not in intimate relationship with the malignant glandular epithelium itself, and (5) endometrial carcinoma with only a patch of squamous cells in glands or on the surface. The term "adenoacanthoma of the endometrium" should be reserved for an endometrial adenocarcinoma in which extensive squamous

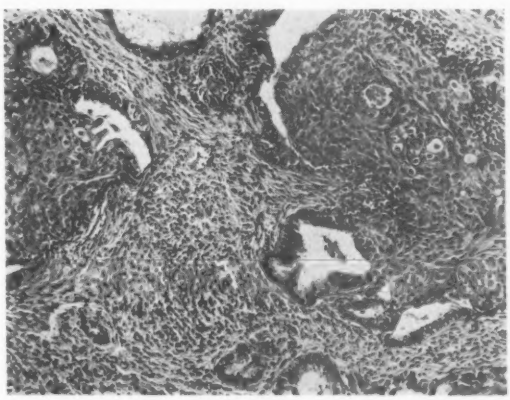


Fig. 3. An illustration of the extensive squamous metaplasia which may be noted in benign endometrial conditions, such as this endometrial polyp. (Hematoxylin and eosin. ×130; reduced ⅓.)

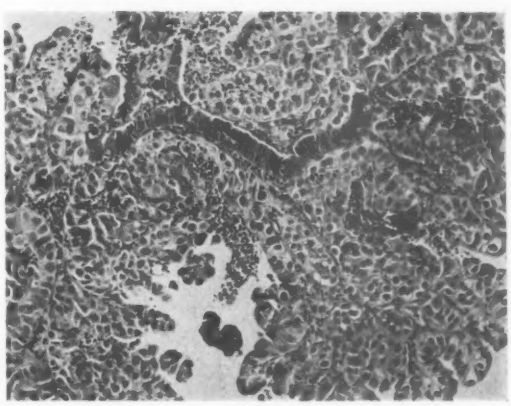


Fig. 4. An endometrial carcinoma with degenerating glandular cells and considerable loss of architecture. Such a lesion, the degenerating cells of which simulate squamous cells, has occasionally been erroneously labeled "adenoacanthoma." (Hematoxylin and eosin. × 130; reduced ⅓.)

metaplasia is noted. Adherence to stringent diagnostic criteria will reveal the true incidence of adenoacanthoma of the endometrium to be low and will also minimize the possibility of misconceptions regarding the characteristics of the lesion.

Origin of squamous cells in the endometrium

Considerable disagreement concerning the histogenesis of squamous metaplasia pervades most discussions, though there now appears to be preponderant support for the origin from basal cells situated beneath the columnar cells of the endometrial glands. Such basal cells, also referred to as reserve or infraepithelial cells, are more readily discernible in the human cervix[56] than in the endometrium. However, the stages of transition between glandular epithelium and mature squamous cells observed in careful study of adenoacanthomas are quite similar to experimentally produced squamous metaplasia of the endometrium in lower species, where evidence of the existence of such basal cells has been offered.

The critical issue concerns the histogenesis of the basal cell. Fluhmann,[14] in discussing theories of origin of squamous metaplasia of the cervix and the endometrium, pointed out 3 possible sources: (1) embryonic cells, (2) adjacent squamous epithelium, and (3) cylindrical or glandular epithelium.

Regarding the first-mentioned possible site of origin, Meyer's studies[44] demonstrated that during the third or fourth month of fetal life the squamous epithelium extends to a high level in the cervical canal and is replaced at the sixth month by columnar epithelium. Meyer believed that basal cells which remain beneath the glandular epithelium during this transitional phase subsequently differentiate into squamous cells. This theory, however, applies mainly to the cervix and cannot explain the occurrence of metaplasia in the fundus which is not covered by squamous epithelium in fetal life. It is also difficult to understand why such embryonic cells are not often demonstrable, and it is equally difficult to conceive of such cells remaining during many years of menstrual life and subsequently producing a metaplastic change.

The theory of origin of the squamous cells as a proliferation of basal cells of adjacent squamous epithelium assumes a horizontal extension of these basal cells so as to insinuate themselves between the glandular epithelium and the stroma without disruption of the glandular cells. Such a situation is difficult to imagine as well as difficult to duplicate experimentally. In addition, squamous metaplasia frequently occurs in glandular areas at a considerable distance from any squamous epithelium and also occurs at the tips of endometrial polyps.

Fluhmann,[12-16] who has extensively studied squamous metaplasia, considers the columnar cells to be the most likely site of origin of the basal cells. The location of the basal cells beneath the glandular epithelium and the occasional occurrence of mucin, a characteristic of columnar cells, imply origin from the glandular epithelium. A direct type of transformation from well-differentiated, specialized glandular cells to squamous cells does not seem possible in the endometrium or in other organs. One must therefore consider that the basal cell probably represents a cell transitional between the columnar cell and the squamous cell and, in addition, that the basal cell represents a body response to trauma or insult. The normal glandular cells appear to be multipotent and capable of differentiation to squamous cells as a result of the proper stimulation.

The squamous cells occurring in the endometrium therefore appear to result from metaplasia of the indirect type. The term "metaplasia" implies that a differentiated tissue is altered both morphologically and functionally in response to environmental changes; in essence, it is a form of abnormal regeneration. The endometrium is subject to various changes (e.g., carcinoma, hyperplasia, endometritis) which cause an indirect metaplasia with transformation of cells derived from specialized glandular cells to cells which are morphologically and

functionally different (i.e., squamous cells). This belief is supported by studies of metaplasia in other human organs following trauma, as well as by the studies of squamous metaplasia in experimental animals.

Material and methods

A group of 348 endometrial adenocarcinomas diagnosed at Stanford University Hospital between 1930 and 1959 were reviewed. Cases previously diagnosed as adenoacanthoma were re-evaluated, and, whenever indicated, additional histologic sections were made. Twenty-four adenoacanthomas of the endometrium were confirmed by examination of the curettings or of the uterus by two or more gynecologic pathologists. In 22 surgically treated patients, the ovaries removed at laparotomy were normal, thereby eliminating the ovary as a possible primary site. In the 2 remaining cases, the lack of ovarian enlargement at curettage (the average size of primary ovarian adenoacanthoma being 11 cm.[9]) and the rarity of ovarian adenoacanthoma compared to the endometrial type would suggest, though not prove, that the endometrium was the primary site. The clinicopathologic features and the results of therapy were analyzed and were also compared to those of previous studies of pure endometrial adenocarcinoma (without squamous metaplasia). Thus, the resemblance to or dissimilarity from pure adenocarcinoma of the endometrium was also determined.

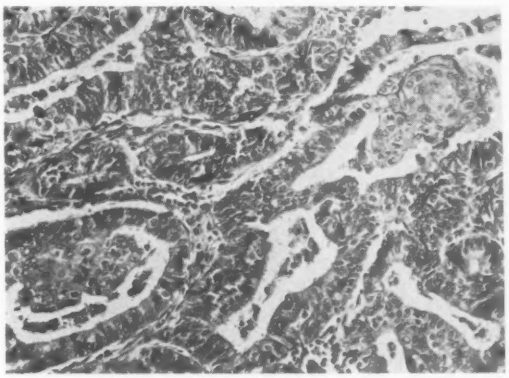
Clinicopathologic features

Incidence. The 24 adenoacanthomas studied were collected from a review of 348 adenocarcinomas of the endometrium, an incidence of 6.8 per cent. In other studies of endometrial carcinoma,[20, 33, 45, 48, 67] the incidence of adenoacanthoma ranged from 1 to 18 per cent.

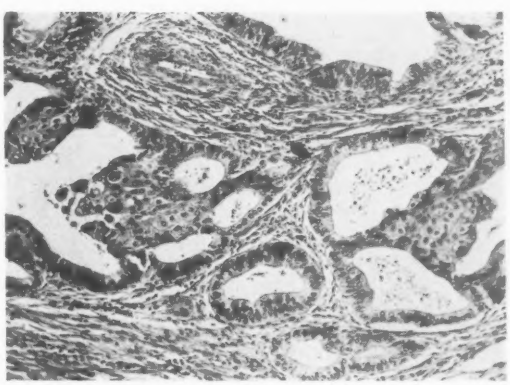
Age. The average age of the 24 patients in this series was 59.6 years with a range of 44 to 75 years. The average age in studies of pure endometrial carcinoma[6, 21, 45, 50, 54, 61, 63] has ranged from 53 to 59 years.

Parity. The incidence of nulliparity is stated to be high in patients with endometrial carcinoma and has been reported[20, 42, 45, 50, 61] to range from 25 to 43 per cent. In this group of adenoacanthomas, 13 (54 per cent) were in nulliparas.

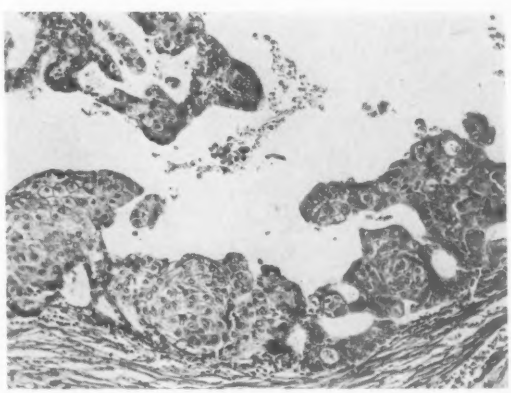
Constitutional factors. Insufficient data in this series of adenoacanthomas precluded



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6



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Figs. 5, 6, and 7. Adenoacanthomas of the endometrium showing various patterns of apparent transition between columnar cells and squamous cells. (Hematoxylin and eosin. ×130; reduced ⅓.)

the accurate statistical evaluation of the factors of obesity, diabetes, and hypertension. There was a distinct impression, however, that these patients demonstrated the trend of higher than expected incidence of obesity, diabetes, and hypertension which has been noted in cases of pure endometrial carcinoma.[23, 52, 58]

Menopause. Only 2 of the patients were premenopausal; their ages were 44 and 53. The remaining 22 patients (91.6 per cent) were postmenopausal. The average age at the time of the menopause was 49 years, which approximates the figures reported for cases of pure endometrial carcinoma.[21, 40, 63] The menopause occurred after the age of 50 years in 9 of the 22 patients, which is suggestive of the trend reported in patients with pure endometrial carcinoma.

Histologic classification. With the exception of one lesion, all the uterine adenoacanthomas were well-differentiated lesions with well-preserved glandular architecture, falling into the histologic Grades I and II of Broders (Figs. 5 and 6). The squamous cells were mature, well-differentiated cells which occasionally demonstrated keratinization or pearl formation. The squamous cells did not reveal malignant characteristics in any of the lesions.

Various stages of apparent transition between columnar cells and squamous cells were noted (Figs. 5, 6, and 7) with frequent protrusion of the squamous cells into the gland lumina. At other times, sheets of squamous cells projected outward from the surface (Fig. 8), and, occasionally, extensive squamous metaplasia was noted between the glands rather than projecting into the gland lumina (Fig. 9).

Myometrial invasion. Of the 24 cases reported here, operation without preliminary irradiation was performed in 17 patients. Of these 17 patients, invasion to at least one third of the depth of the myometrium was demonstrated in 12. Of the 5 patients who received preoperative irradiation, there was significant myometrial invasion in 3. Thus, 15 of 22 patients (68 per cent) demonstrated significant myometrial invasion.

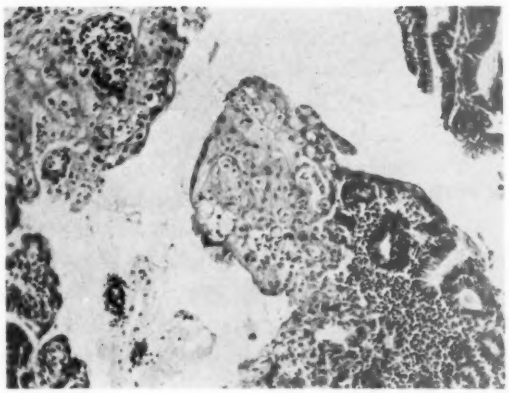


Fig. 8. Adenoacanthoma of the endometrium showing sheets of squamous cells projecting from the surface of the lesion. (Hematoxylin and eosin. ×130; reduced ⅓.)

The incidence of myometrial invasion in pure endometrial carcinoma has been recorded by others[36, 45, 53, 57] in the range of 52 to 65 per cent.

Spread beyond the uterine corpus. The incidence of cervical involvement in pure endometrial carcinoma has been reported as 9 per cent[42] and 10.7 per cent.[27] In this series of adenoacanthomas, 6 (25 per cent) demonstrated histologic evidence of spread to the cervix in the surgical specimen. Vaginal metastasis in endometrial carcinoma has been recorded in 10.4 per cent,[25] 12.1 per cent,[41] and 13.7 per cent[65] according to three studies. In this group of adenoacanthomas, no patient demonstrated vaginal involvement on initial examination. A vaginal metastasis was subsequently noted in only one patient who was treated solely by radium irradiation.

None of the surgically treated patients (22 of 24) had demonstrable ovarian or tubal metastases. In a collected group of 1,375 endometrial carcinomas,[25] ovarian metastasis was noted in 6.8 per cent and tubal metastasis in 2.7 per cent.

Compared to those in the studies of pure endometrial carcinoma cited above, these uterine adenoacanthomas had a higher incidence of cervical spread which was statistically significant according to the chi square test. No significant difference was noted, however, in the incidence of vaginal, ovarian,

or tubal metastases. This study therefore failed to confirm the reported observation [26, 65] that adenoacanthoma is associated with a higher incidence of vaginal metastasis than pure endometrial carcinoma.

Although no ovarian metastases were demonstrable in any of the surgically treated patients in this series, there have been several reports of uterine adenoacanthoma with ovarian metastases.[2, 8, 9, 32, 59] In certain cases of simultaneous endometrial and ovarian adenoacanthoma, it is impossible to determine the primary site of origin. Parenthetically, it should be noted that the patients in a number of reported cases of the rare primary ovarian adenoacanthoma had neither a curettage nor a hysterectomy so that it is impossible to rule out the endometrium as the primary site of origin. In 4 of the cases of simultaneous ovarian and endometrial adenoacanthoma,[29] the ovarian lesion was known to be bilateral. Although the possibility exists that an unknown stimulus may produce an adenoacanthomatous change in both the uterus and the ovaries, one would be more inclined, as Kistner and Hertig[29] suggested, to incriminate the uterus as the primary site of origin in these 4 cases with endometrial and bilateral ovarian involvement.

None of the uterine adenoacanthomas in this series demonstrated extrapelvic metastases. Such cases have been reported, however, in the literature. Meigs[42] reported an adenoacanthoma of the endometrium with metastases to the axillary nodes, and Stein and Torek[62] described a similar lesion with histologic evidence of spread to the posterior mediastinum and lungs. Doko[10] reported a metastatic adenoacanthoma in which the squamous cells were recognizable in a lung specimen removed 11 years later and again in widespread recurrent lesions observed at autopsy 16 years later. Herbut[22] similarly noted an endometrial adenoacanthoma in which both the primary lesion and the metastases to the abdominal nodes revealed not only glandular elements but also benign squamous cells.

Garnet and Crane[18] reported an interesting case of ovarian adenoacanthoma in which there was postoperative recurrence in the supraclavicular nodes and vertebrae. The metastatic tumor was composed entirely of malignant squamous cells. This case report is significant when compared to that of an endometrial adenoacanthoma reported by Novak and Nalley[51] in which the squamous component on curettage presented cells with distinct malignant characteristics. A cervical biopsy had been negative for squamous cell carcinoma. Operation revealed tumor involving the adnexa, omentum, and regional nodes. These latter 2 cases suggest the possibility that the squamous component in both endometrial and ovarian adenoacanthomas may on rare occasions undergo malignant change with distant metastases of these squamous cells. One would be obliged, however, when encountering such cases, to exclude the possibility of cervical carcinoma or the rare primary squamous cell carcinoma of the corpus.

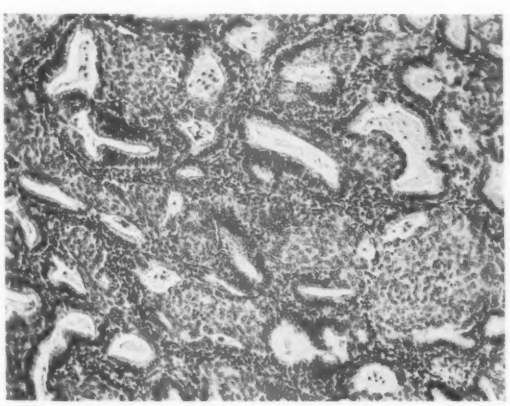


Fig. 9. Adenoacanthoma of the endometrium showing extensive squamous metaplasia occurring predominantly between the glands rather than projecting into the gland lumina. (Hematoxylin and eosin. ×130; reduced ⅓.)

Treatment and results

All 24 patients in this series were treated; 17 were treated by hysterectomy and bilateral salpingo-oophorectomy, 5 by preoperative irradiation and operation, and 2 by irradiation alone. Eight of the 24 patients were treated within the past 3 years and are living and well. The remaining 16 pa-

tients were eligible for 5 year follow-up. A 100 per cent follow-up of these 16 patients was obtained, and the 5 year survival rate was 75 per cent.

In the group of 17 patients treated by a surgical procedure alone, 8 of the 9 eligible for 5 year follow-up are living and well. In the group of 5 patients treated by intrauterine radium irradiation prior to hysterectomy with removal of the adnexa, 4 are living and well 5 or more years. Of the 2 patients treated solely by irradiation, one received an initial intrauterine application of radium followed by a second application one year later for vaginal recurrence. This patient died 23 months after the initial treatment. The other patient received one radium application and died 28 months later of metastatic carcinoma.

The over-all survival rate of 75 per cent in 16 of the 24 patients of this series is comparable to the 5 year survival rate reported for pure endometrial carcinoma. These figures do not support the contention that adenoacanthoma has a significantly better prognosis than pure endometrial carcinoma, nor do they indicate a poorer outlook, as some authors have suggested. The prognosis in adenocarcinoma of the endometrium actually appears to be unaltered by the presence of squamous metaplasia.

Summary

1. The term "adenoacanthoma of the endometrium" should be reserved for an adenocarcinoma with extensive squamous metaplasia. Specific studies of this lesion are rare, and diametric opinions exist on several aspects, including the prognosis compared to the ordinary endometrial carcinoma.

2. The squamous cells in adenoacanthoma are similar to the metaplastic change manifest in various benign endometrial conditions in the human and in experimental lesions in animals. The mature, well-differentiated squamous cells appear to arise from basal cells derived from the glandular epithelium as a regenerative response to injury.

3. Twenty-four adenoacanthomas were noted in a review of 348 endometrial carcinomas, an incidence of 6.8 per cent. A high incidence of nulliparity and a tendency toward a late menopause were noted, both of which have also been reported in patients with pure endometrial carcinoma.

4. All but one of the lesions were well-differentiated adenocarcinomas. Compared to those in previous studies of pure endometrial carcinoma, these cases presented a significantly higher incidence of extension to the cervix. No significant difference was noted, however, in the incidence of myometrial invasion or metastasis to the vagina, ovaries, or tubes.

5. Hysterectomy and bilateral salpingo-oophorectomy was the treatment in 17 patients, preoperative irradiation and operation in 5 patients, and irradiation alone in 2 patients. In 16 patients eligible for 5 year follow-up, the survival in all 3 groups was 75 per cent, a figure comparable to the survival rate in cases of pure endometrial carcinoma. It therefore seems that there is no basis for the diametric statements that patients with adenoacanthoma have a significantly better or poorer prognosis than those with pure endometrial carcinoma. It would appear that the prognosis in adenocarcinoma of the endometrium is unaltered by the presence of squamous metaplasia.

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Incidence of adenomyosis in patients with endometrial adenocarcinoma

A study of 100 patients

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GIAMMALVA and Kaplan[5] studied the tissue from 120 patients with endometrial adenocarcinoma and 264 patients without this disease. They found the incidence of endometriosis interna (i.e., adenomyosis) to be 33 per cent in the former and only 18 per cent in the latter group. These authors interpreted their findings to suggest a possible common etiological factor for both adenomyosis and endometrial carcinoma. They did not postulate as to the nature of this factor. They also cited one previous study[4] which apparently supported their findings.

To make the diagnosis of "endometriosis interna" (i.e., adenomyosis), Giammalva and Kaplan[5] required the "presence of ectopic non-neoplastic endometrial glands and stroma in the myometrium, well within the muscle wall."

In the literature devoted to adenomyosis and endometrial adenocarcinoma, there are but few papers containing data pertinent to coexistance or etiological relationship of the two lesions. Figures from these studies are presented in Table I and are noted below.

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The work of Fahlund and Broders on postmenopausal endometrium is the best suited for comparison with Giammalva and Kaplan's study. Although Fahlund and Broders did not record adenomyosis as such, they did classify "subbasal (endometrial) glands" according to their density and their depth in the myometrium; their "grade 4" subbasal glands were described as "well down into, and surrounded by, myometrium . . . similar to glands found in cases of adenomyosis." This description, it is noted, is quite similar to Giammalva and Kaplan's criterion for the diagnosis of adenomyosis. Fahlund and Broders reported "grade 4" subbasal glands in 16 per cent of 100 noncancerous control cases, but in only 8 of 86 cases of adenocarcinoma (9 per cent). Giammalva and Kaplan stated that Fahlund and Broders found subbasal glands in 58 of their 86 cases of adenocarcinoma. However, in referring to Fahlund and Broders' article, we could find mention of subbasal glands (all grades, 1 through 4) in only 28 cases of cancer; further, only the 8 cases cited above are deserving of our attention by virtue of having "grade 4" glands.

Taylor's series,[8] as originally described in his article, contained 138 cases of carcinoma of the corpus. However, for purposes of comparison we have eliminated 12 cases in which only biopsy or curettage material was available for study and another 21 cases in which the absence of any lining endome-

trium in the sections made the diagnosis of adenomyosis questionable. Of the remaining 106 cases, 8 per cent were associated with adenomyosis. Again, however, the author's diagnostic criteria were not stated.

In an effort to show the great difference in reported incidence of adenomyosis in all cases, we have included a brief comment on two other series and have included them in Table I for comparison.

Hunter and associates,[6] in a series of 1,856 consecutive hysterectomies for all causes, including cancer, noted adenomyosis in 28 per cent of their cases. For the diagnosis of adenomyosis they required the presence of islands of endometrial glands separated from the lining endometrium by at least two low-power fields, plus muscular hyperplasia. Dreyfuss,[3] however, in his similar series of 1,807 consecutive hysterectomies for all causes, noted only 8 per cent adenomyosis; unfortunately, he did not mention his criteria for the diagnosis.

Materials and methods

The material examined in this study was obtained from files in the laboratory of the Department of Obstetrics and Gynecology of Northwestern University Medical School. Only surgical specimens were used in this study; tissue obtained via autopsy or biopsy was not employed. Further, only uteri with at least two blocks of corpus tissue available for examination were used in this study; however, many uteri had more than two blocks.

Two groups of uteri were selected: those with endometrial adenocarcinoma and those without. For the carcinoma group, only uteri with the diagnosis of unequivocal adenocarcinoma were used; uteri diagnosed as "probable" adenocarcinoma, adenocanthoma, and carcinosarcoma, for example, were unacceptable. Also, sections made useless by extensive invasion of tumor into the myometrium were not included. The most recent 100 consecutive cases of endometrial adenocarcinoma that satisfied all the above-stated requirements were then selected. The age of each patient (except one noted below) at the time of hysterectomy was recorded, and the cases were divided into 5 year age groups (Table II). The age of one patient could not be determined.

For the noncarcinomatous control group, 100 uteri removed for any cause other than endometrial adenocarcinoma were selected as follows: starting with letter "A" in the alphabetized file, we took the first 3 cases suitable for our control group in the 40 to 44 age group, the first 9 cases in the 45 to 49 age group, and so on until each 5 year bracket of the cancer group had been matched with an equal number of control patients (Table II). In this way, the carcinoma and control groups were matched with respect to age distribution. To account for the one cancer patient of unknown age, one extra control case was placed in the 50 to 54 age group, the largest single age group in the study.

To make the diagnosis of adenomyosis, we required the presence of islands of normal-appearing endometrial glands and

Table I. Prevalence of adenomyosis in various studies

	Uteri removed for					
	All causes		*Carcinoma*		*All causes other than carcinoma*	
Investigators	*No. cases*	*Per cent of adenomyosis*	*No. cases*	*Per cent of adenomyosis*	*No. cases*	*Per cent of adenomyosis*
Hunter and associates[6]	1,856	28	---	---	---	---
Dreyfuss[3]	1,807	8	---	---	---	---
Taylor[8]	---	---	106	8	---	---
Fahlund and Broders[4]	---	---	86	9	100	16

Table II. Age distribution of cancer and control groups in present study, showing prevalence of adenomyosis

	Cancer group		*Control group*	
Age groups	*Total cases*	*Cases of adeno-myosis*	*Total cases*	*Cases of adeno-myosis*
40-44	3	0	3	0
45-49	9	1	9	3
50-54	17	4	17	2
55-59	33	3	34	11
60-64	15	2	15	6
65-69	16	4	16	5
70 and above	6	2	6	1
Unknown	1	0	---	---
Total	100	16	100	28

Table III. Comparison of present study with that of Giammalva and Kaplan

	Cancer group		*Control group*	
Investigators	*No. cases*	*Per cent of adeno-myosis*	*No. cases*	*Per cent of adeno-myosis*
Giammalva and Kaplan[5]	120	33	264	18
Roddick and Johnson	100	16	100	28

stroma within the myometrium, separated from the lining endometrium by at least one low-power field.[2]

All slides were reviewed by both authors, who individually recorded the presence or absence of adenomyosis. Unlike Giammalva and Kaplan, we made no attempt to record the "degree" of adenomyosis or to correlate the presence or absence of adenomyosis with the degree of differentiation of the tumor.

Results

Adenomyosis was found to be present in 28 of the 100 cases in the control group, but in only 16 of the 100 in the cancer group (Table II). Statistical analysis with the chi-square formula gave a value of 4.20 for χ^2—i.e., a likelihood of duplication of the results by chance of 1 in 20. This figure is of questionable statistical significance.

Comment

At a glance (Table III), it can be seen that our findings do not agree with those of Giammalva and Kaplan. It may well be that the main difference in these two sets of results stems from a difference in criteria for the diagnosis of adenomyosis. We have tried to be as objective as possible by using a readily definable unit of measurement (i.e., one low-power field from the endometrium), which they did not do. Therefore, the two studies may not be truly comparable.

Another factor which may or may not be significant in comparing these studies is the racial and socioeconomic composition of the various groups. We became interested in this factor while trying to explain the varied findings of Hunter and associates[6] and Dreyfuss[3] (Table I). Hunter and associates, who, it is recalled, required a space of two low-power fields plus muscular hyperplasia to make the diagnosis of adenomyosis, found adenomyosis in 28 per cent of their cases. Dreyfuss' criterion, although not stated, would not be expected to be more stringent than Hunter's; yet Dreyfuss found adenomyosis in only 8 per cent of his cases. We found it difficult to resolve these different findings on the basis of criteria alone; therefore, we searched the literature for any reference to a racial or socioeconomic pattern in adenomyosis. Although reports of decreased prevalence of (external) endometriosis in Negro and charity patients are numerous,[1, 7, 9] we were unable to find any clear-cut evidence for suspecting a similar tendency in adenomyosis.

We were unable to demonstrate an increased prevalence of adenomyosis in endometrial carcinoma. Do our figures indicate a *decreased* prevalence of adenomyosis with endometrial carcinoma? Not necessarily; for, as Giammalva and Kaplan pointed out, if adenomyosis and endometrial carcinoma are etiologically unrelated, one would actually expect to find a greater percentage of adenomyosis in the control group than in

the carcinoma group. To explain, let us assume, for sake of discussion, that the occurrence of adenomyosis along with endometrial carcinoma is completely coincidental, i.e., that the two conditions are totally unrelated. With this assumption, the percentage of adenomyosis in our cancer group should be the same as the percentage of adenomyosis in the general population. On the other hand, our control group, which is made up of women over 40 years of age with a variety of gynecologic problems severe enough to necessitate hysterectomy (including adenomyosis), would be expected to have a greater percentage of this condition than that found in the general population (and, it follows, greater than that found in our cancer group). How much greater cannot be stated; suffice it to say that the greater percentage of adenomyosis in our control group does not imply a *decreased* prevalence of adenomyosis associated with endometrial carcinoma.

Summary

Slides from 100 patients with endometrial adenocarcinoma and 100 age-matched patients without were examined; adenomyosis was found in 16 per cent of the cases of carcinoma and in 28 per cent of the control cases.

A possible explanation for the greater percentage of adenomyosis in the control group was given.

These data cannot be interpreted to indicate an increased prevalence of adenomyosis in uteri containing endometrial carcinoma, nor do they give credence to a postulated common etiological background for the two conditions.

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Carcinoma arising in adenomyosis associated with a feminizing mesenchymoma of the broad ligament

A case report

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ADENOMYOSIS is defined as a benign invasion of the endometrium into the uterine musculature, associated with a diffuse overgrowth of the latter. This ectopic endometrium is often referred to as endometriosis interna or uterina. In discussing diffuse adenomyosis, Novak and Novak stated that "although atypical hyperplasia is common in the deep islands of aberrant endometrium, it is astounding how infrequently primary adenocarcinoma is found in this area."[1] These authors have seen two recognizable cases, one in their laboratory and the one reported herein.[1] Both specimens demonstrated a normal surface endometrium with an adenocarcinoma occurring in an island of hyperplastic adenomyosis. Another unusual finding in the following case report is that of an extraovarian feminizing mesenchymoma (granulosa-theca cell tumor).

Mrs. E. T., a 48-year-old Negro woman, gravida ii, para i, who had had 1 abortion, was first seen in 1947 with the chief complaint of menometrorrhagia of 18 months' duration. The right tube and ovary had been removed elsewhere 17 years previously. The reason for the operation was unobtainable. For the month prior to admission, vaginal bleeding had been continuous, with the passage of large clots. Pelvic examination revealed a healthy cervix, and the uterus was enlarged symmetrically and was twice the normal size. The left tube and ovary were not palpable. Physical examination revealed such essential hypertension that a major operation was thought to be contraindicated. The hemoglobin level was 36 Gm. per cent. Following blood replacement, a dilatation and curettage was performed and intracavity radium was applied for a dosage of 2,400 mg. hr. The pathologic diagnosis was endometrial hyperplasia (Fig. 1).

Intermittent vaginal bleeding continued during the next 4 years. Three curettements, at intervals of 9 to 14 months, resulted in specimens that showed only fragments of endometrial glands and strands of fibrin and debris. Since the persistent bleeding required definitive therapy, a dilatation and curettage, total hysterectomy, and left salpingo-oophorectomy were performed in October, 1952. The uterus was one and one-half times normal size with a cavity depth of 4.5 cm. No circumscribed tumor was present but one or two areas of the incised uterine wall closely resembled diffuse adenomyosis. The left Fallopian tube and ovary were atrophic. Just beneath the medial end of the left utero-ovarian ligament a small yellow, rubbery retroperitoneal tumor was attached to the lateral uterine wall. The tumor measured 1.5 by 1 by 1 cm. It was encapsulated and the cut surface was smooth and yellow in color.

Pathology report. The specimen consisted of curettings, uterus, left tube and ovary, and a 1.5 by 1 by 1 cm. yellow tumor that was adherent to the left lateral uterine wall between the layers of the broad ligament. The uterus measured 9

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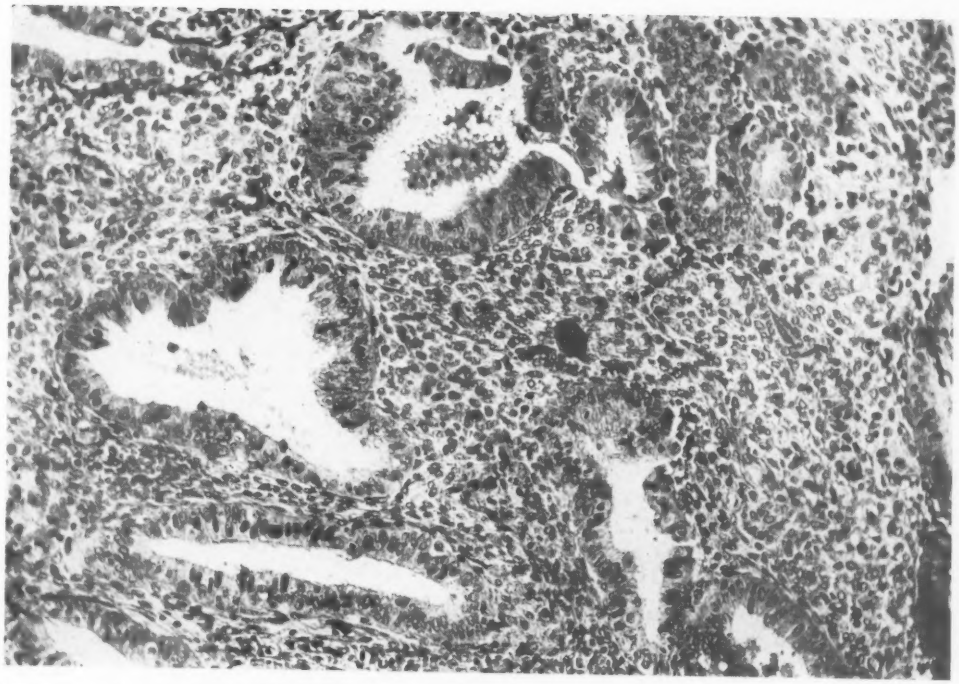


Fig. 1. Sections of curettings obtained 5 years before hysterectomy, showing areas of atypical endometrial hyperplasia. (Hematoxylin and eosin. ×125; reduced ¼.)

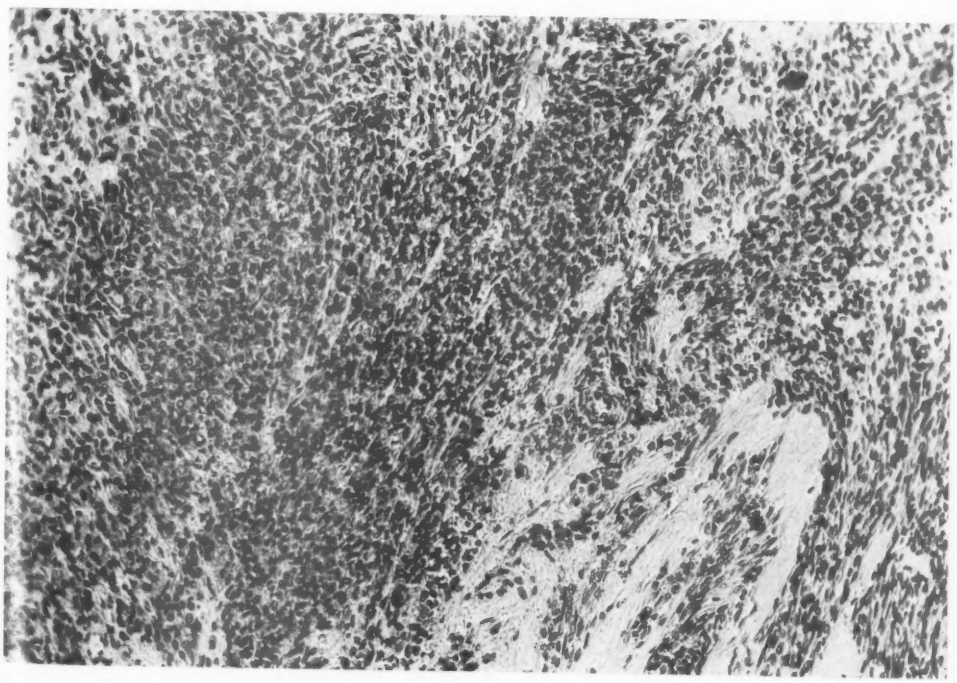


Fig. 2. Photomicrograph of the yellow encapsulated piece of tissue found in the left broad ligament. (Hematoxylin and eosin. ×190; reduced ¼.)



Fig. 3. Section of uterine wall demonstrating adenomyosis. The circle indicates the area of carcinoma. (Hematoxylin and eosin. ×7; reduced ⅓.)

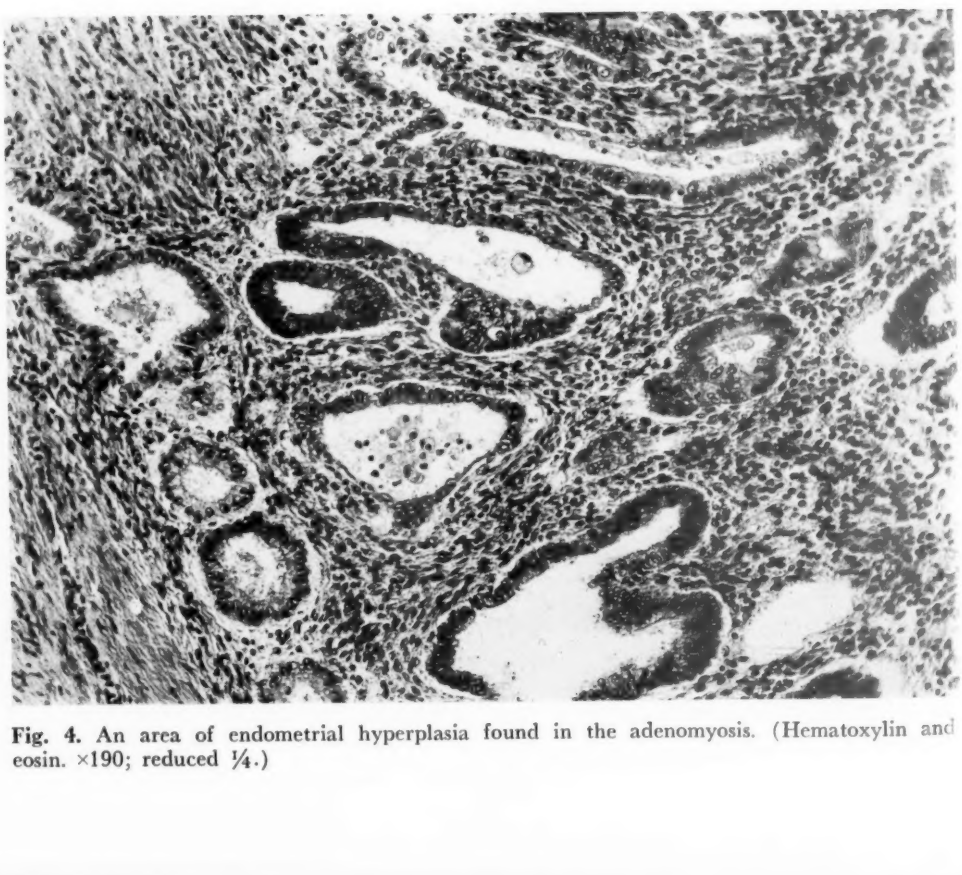


Fig. 4. An area of endometrial hyperplasia found in the adenomyosis. (Hematoxylin and eosin. ×190; reduced ¼.)

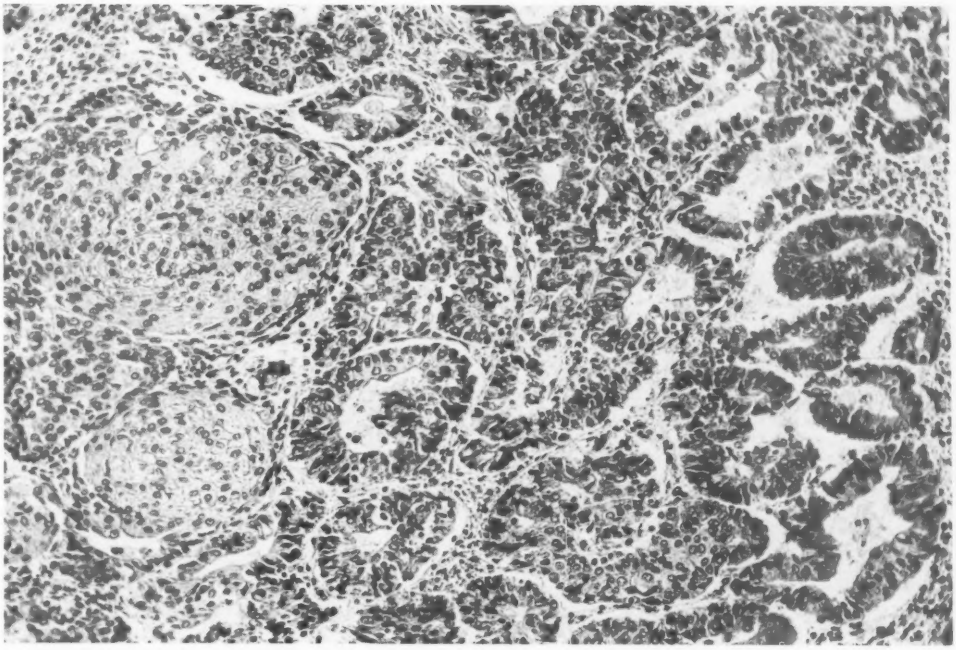


Fig. 5. Photomicrograph of carcinoma present in the adenomyosis. Squamous metaplasia is also seen. (Hematoxylin and eosin. ×190; reduced ¼.)

by 7 by 5 cm. and had been opened anteriorly. The endometrial cavity was 4.5 cm. in depth and had been curetted.

In the fundus and cornua there remained shaggy areas of endometrium, 4 mm. in thickness, velvety and hemorrhagic, but not friable. The thickest portion of the anterior wall contained a soft area approximately 2 by 1 by 1 cm. which was filled with velvety, pale, nonfriable tissue, grossly resembling endometrium.

Microscopic examination. The glands were large and cystic and were lined with columnar epithelium, with some pseudostratification of the glandular cells. The stroma was relatively loose in texture. A careful search of all the tissue revealed no unripeness or dedifferentiation of cells.

The left ovary showed no evidence of stromal hyperplasia. The over-all appearance was one of atrophy. There were a number of small inclusion cysts present. The left tube was not remarkable.

The small nodule noted in the broad ligament was composed of interlacing bundles of spindle cells peripherally and of masses of rounded cells with more or less spherical nuclei and a moderate amount of rather eosinophilic cytoplasm. In a few areas there was a suggestion of rosette formation but nothing definite. The rounded cell elements were seen to be invading lymphatics and several large masses of such cells were present within large perivascular lymphatics outside the margin of the nodule (Fig. 2).

Throughout the uterus were seen islands and strands of endometrial glands and stroma (Fig. 3). The glandular elements were for the most part regular but in several areas the nuclei of the glands were enlarged and showed pleomorphism and stratified cells. In one area there was loss of normal glandular pattern. Cords of epithelial cells were present which must be considered carcinoma. There were in addition small areas of squamous metaplasia (Figs. 4 and 5).

Diagnoses: adenomyosis of uterus; carcinoma arising in adenomyosis of uterus; feminizing mesenchymoma (granulosa-theca cell tumor) of broad ligament, left ovary, and tube.

These microscopic sections were reviewed by Dr. Ronald R. Greene who concurred in this interpretation.

This patient died at home within the year following this operation. The cause of death according to her family physician was cardiac disease. No autopsy was performed.

Comment

Carcinoma arising in endometriosis of the ovary and endometrial sarcoma arising from

areas of endometriosis have been documented.[2-4] Dockerty, Pratt, and Decker[5] and Lash and Rubenstone[4] have reported instances of primary adenocarcinoma of the rectovaginal septum arising from endometriosis. These carcinomatous transformations are extremely rare. It is interesting to speculate that the feminizing mesenchymoma of the broad ligament in this case secreted estrogens to produce the endometrial hyperplasia and to stimulate the development of adenomyosis with its subsequent malignant transformation. The association of a feminizing mesenchymoma and endometrial carcinoma has been discussed at length in several papers. Over 132 instances of these combined tumors have been reported.[6] An instance of an extraovarian granulosa-theca cell tumor in the broad ligament associated with an adenocarcinoma of the endometrium has been mentioned in a study by Chung.[7] Whether or not these feminizing mesenchymomas incite the development of endometrial cancer is controversial. Ten to 27 per cent of these ovarian tumors have been found associated with adenocarcinoma of the endometrium in some series.[8, 9]

Summary

An instance of carcinoma arising in an area of adenomyosis associated with a feminizing mesenchymoma of the broad ligament is reported.

I am grateful to Dr. Horatio T. Enterline for reviewing this material.

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Changing ratio of cervical to corpus carcinoma

A 32 year survey

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THIS report was initiated originally as the result of what I thought was a true changing incidence of cervical to corpus cancer of the uterus in my own material. There were several reasons for this impression. First was the increase in material which I have seen each year with an apparent increase in corpus cancer in women before the menopause. Second, the figures given in the literature 10 or more years ago showed an incidence of cervical to corpus cancer ranging from 10:1 to 5:1, which figures had become accepted and fixed in my mind and I had not made a study of our own cases. Third, the establishment of Papanicolaou smears and conization procedures over the past 10 years in our hospital has focused our attention on cervical cancer, revealing a very definite decrease in invasive cervical cancer as compared to corpus carcinoma. All of these facts have tended to enhance our interest in uterine cancer in general.

Prior to 1951, figures given by Rock,[1] Schiller,[2] Illingworth and Dick,[3] and others quoted the incidence of cervical to uterine corpus malignancy as 10:1. During this same period, other figures given were 7:1, 6:1, and 5:1.[4-6] Since 1951, quite a substantial reduction to 3:1 and even lower has appeared.[7-9]

There has been much speculation regarding the possible reasons for this changing occurrence of the 2 uterine cancers, and many questions arose as to possible explanations. Some of the following might be considered: Are women living longer, bringing them into the age for endometrial cancer? There are several studies to bear out such an assumption.[10] Is better postpartum management of the cervix decreasing the incidence of cervical cancer? Is more attention paid to treatment of erosions and other benign cervical lesions? Is the great publicity given to the early signs of cancer in some manner responsible for the changing percentages? Is our diagnostic acumen becoming more acute? Has the fact that the services of a qualified pathologist are more generally used throughout most small hospitals as a result of the efforts of the American College of Surgeons and, more recently, the Joint Commission on Accreditation of hospitals had anything to do with this altered ratio? Has the increase in the use of female sex hormones varied the total percentages of the two cancers? There is controversy concerning exogenous estrogenic stimulation as a causative agent of endometrial carcinoma. However, there does seem to be an increasing collection of data which suggests that fundal cancer may be related to long, drawn-out, noncyclic ovarian hormonal activation of the endometrium. Has our former conception of the microscopic diagnosis of fundal cancer changed and are pathologists diagnosing as cancer such histologic abnormalities as endometrial polyps, cystic and adenomatous hyperplasias, certain regressive atypicalities, and even so-called carcinoma in situ of the endometrium? It is quite true that a few women have developed fundal carcinoma after repeated curettage for bleeding or other rea-

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sons over a period of years. Histologic studies have shown progressive abnormal changes as those just mentioned which finally eventuated in classical clinical endometrial cancer.[11, 12] Moreover, similar microscopic variants are not too rarely encountered in endometrium containing unqualified adenocarcinoma. It is likely that carcinoma probably does not often spring de novo from normal endometrial glands but from a series of more or less atypical hyperplastic localized or widespread growth changes. Furthermore, such abnormalities do not necessarily indicate incipient cancer since probably only a small fraction ultimately become clinically malignant.

The foregoing are but a few of the questions that have been or could be raised to suggest an explanation for this change in relative proportions of the two cancers as reported in the literature.

The present study covers 32 years in the experience of one pathologist, except for 3½ years during World War II. A total of 1,608 cases of cancer of the corpus uteri and cervix are tabulated. The figure of cervical carcinoma is broken down into 729 invasive cervical cancers and 307 carcinomas in situ. Sarcomas, mesodermal mixed tumors, and malignancies of chorionic origin were all deleted. The cases were drawn from St. Luke's Hospital, in Kansas City, Missouri, and smaller hospitals throughout the states of Kansas and western Missouri and a very few from northern Oklahoma and southern Nebraska.

All but a very few of the carcinomas in situ of the cervix have been studied in the past 10 years. Prior to this time, these few were captioned intraepidermal carcinoma, cervices with atypical hyperplasia, changes in cell type, or early noninvasive cancer. Prior to this 10 year period, only 23 cases would now be classified as carcinoma in situ. Since 1950, with the advent of a steadily increasing use of the Papanicolaou smear of the cervix, we have diagnosed cervical carcinoma in situ or carcinoma in situ with gland penetration in 284 cases. The incidence has steadily increased from 16 cases in 1950 to 44 cases in 1959, with the exception of the year 1956 in which we studied 59 cases. The figures for the decades are presented in Table I.

Table I

Years	*Cervix*	*Corpus*	*Ratio*
1928-38	133	62	2:1 +
1938-48	204	135	2:1 −
1948-60	695*	378	2:1 −
	396†	(378)	1:1 +
	299‡	(378)	1:1 −
Total (1928-1960)	1,036§	572	2:1 −

*Invasive and in situ.
†Invasive.
‡In situ.
§Including in situ carcinoma.

Table I would seem to indicate, if carcinoma in situ is included, that there has been no statistically significant change in the incidence of corpus and cervical cancer in the past 32 years. Moreover, it might be argued that in the past 10 years, the use of the Papanicolaou smear and biopsy or cold knife cone (all of these cases of in situ carcinoma were diagnosed by biopsy or conization, often with subserial sections of the latter) had practically cut the incidence of invasive carcinoma from a previous ratio of 2:1 to a figure approaching 1:1, with a similar ratio of roughly 1:1 for in situ carcinoma of the cervix and corpus carcinoma. Certainly, by the employment of Papanicolaou smear, and biopsy or conization of the cervix in those patients with positive smears, we are finding cases of cervical cancer many years earlier. Such an argument would suggest from these studies that the intraepidermal, in situ or Stage 0 carcinoma of the cervix, as far as this statistical analysis is concerned, might represent a true stage of early cervical carcinoma.

Therefore, from this point of view, the reported changing incidence of cervical and corpus cancer would not be borne out in our material. On the other hand, if we delete cervical cancer in situ for the last decade from the series of cervical cancer, it would mean an incidence reduction of can-

cer of the cervix to cancer of the endometrium from 2:1 to 1:1. More properly, therefore, it should be argued that this change in incidence was genuine and not apparent, since practically none of the cases of carcinoma in situ of the cervix showed gross lesions or symptoms suggesting cancer, many were completely negative grossly, and the great majority were symptomless. Furthermore, the age incidence of this group was roughly 10 or more years younger than that of patients with invasive cervical malignancy—average age: in situ, 36.6 years; invasive, 48.6 years.[13] A significant number of women were under 30 years of age, and many were in the middle and early 20's. It should also be noted that the incidence of carcinoma in situ of the cervix in the first 2 decades of this survey was practically negligible as far as having any statistical influence on the ratio of cancer of the cervix to cancer of the fundus.

Table II

Years	*Cervix*	*Corpus*	*Ratio*
Post mortem			
1935-1942	55	11	5:1
1950-1957	68	5	12:1 +
Surgical			
1935-1942	149	31	5:1 −
1950-1957	184	29	6:1 +

Admittedly, these 1,608 cases constitute a small series, but they do represent the findings of one pathologist in a fairly good cross section of hospital patients drawn from rural and small town areas and a large city in the mid–United States where the type of patient is more or less the same, being largely old stock, native American, private patients. Only a very few were Jewish and few, if any, were Negroes. It has been established that there is a much lower rate of cervical cancer in Jewish women and a higher incidence in Negroes.[14] Hence these racial factors do not influence our figures. Furthermore, statistical studies have been reported that tend to show that cancer of the cervix uteri is increased in patients of low economic status.[15] This association might have some influence in explaining the discrepancy in our figures for the first 20 years of this study as compared to the reported incidence of cervical to corpus during that same period of time, since most of our patients were private patients in private hospitals and, therefore, in a moderate to better than moderate economic bracket.

The racial and economic status factors become most apparent when we compare the figures from the Kansas City Municipal Charity Hospital. Dr. Charles Wheeler, pathologist at this institution, has kindly furnished me with figures covering two 8 year periods, namely, both necropsy and surgical pathology numbers for the years 1935 through 1942 and 1950 through 1957, which are given in Table II. We have not included Dr. Wheeler's in situ carcinomas since these cases would have the same lack of statistical significance as our own. No record was obtained in those cases regarding the number of Negroes, but a great many of these patients were Negro.

It will be noted that aside from the necropsy figures for the period 1950 through 1957 when the ratio of cervical to corpus cancer was roughly 12:1, there was no significant change in ratio from 5:1 or 6:1 for the two periods. We must, therefore, conclude that race and economic status are potent factors in the changing ratio as observed in our figures for private patients as opposed to those from a large charity hospital. It should also be mentioned that in our own material only surgical pathology cases were included.

In going over our own cases, I was impressed by the fact that we are seeing much less advanced corpus cancer than we did 25 to 30 years ago, and the same holds true for advanced Stage III and Stage IV cervical carcinoma. This could possibly be explained as being due to better education of both patients and physicians.

Summary and conclusions

1. A 32 year survey of 1,608 cases of cancer of the cervix and endometrium is pre-

sented. For the first 2 decades of this study, the ratio of cervical to fundal cancer was roughly 2:1. This figure was quite different from many reports in the literature for this same period, which ranged from 10:1 to 5:1, as well as from a survey of similar cases from a large local municipal charity hospital.

2. The possible reasons for this discrepancy, such as geographic location and race and economic status, were mentioned.

3. Following 1951, a decrease in published figures from 10:1 to 3:1 of cervical cancers to corpus cancer was noted, and some of the possible reasons for this change are discussed.

4. In our survey, a significant drop in ratio of invasive cervical cancer to endometrial cancer from 2:1 to 1:1 was observed since 1948.

5. The influence of a steadily increasing employment of routine Papanicolaou stains on all cervices with biopsy or conization of all patients with positive smears is discussed, and the ratio of in situ carcinoma of the cervix to carcinoma of the fundus was found to be almost 1:1. Statistically, this figure, when combined with a 1:1 ratio for invasive cervical cancer, might suggest that carcinoma in situ is a genuine, preinvasive stage of invasive cancer.

6. A quite definite decrease in advanced cervical and endometrial cancer in our material is pointed out.

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Urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele, and prolapse

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STRESS incontinence is a very difficult symptom to relieve surgically. The operation of Marshall, Marchetti, and Krantz[1] is the brightest spot in this otherwise dismal picture. Certainly the results[2, 3] from this operation are superior to those achieved by other procedures. However, the Marshall-Marchetti-Krantz operation is not always easy to perform, the field is often deep and bloody, the edges of the urethra are difficult to define, and the periosteum on the posterior aspect of the symphysis is far from ideal as a holding structure.

In attempting to overcome some of these difficulties, we inserted the finger of the left hand into the vagina as the dissection in the space of Retzius was being made with the right hand. This gave the great advantage of bimanual palpation and was of much help in defining the structures and in doing the suturing. This maneuver, however, had its drawbacks as it required frequent changing of the left glove in order to maintain asepsis. This disadvantage stimulated the idea of a double drape arrangement with a sterile glove inserted into the vagina and its cuff sutured to the surrounding drapes. With this arrangement, it is possible to insert the fingers of the left hand into the vagina without fear of bacterial contamination. In passing, it is noteworthy that in the many cases in which this method has been employed, infection has not been a problem.

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Operative technique

One day, while we were doing a Marshall-Marchetti-Krantz operation, the sutures in the periosteum continued to pull out and it was necessary to look for another point of attachment. An examination of the field revealed that the intravaginal finger was pushing the anterior vaginal wall up to a level as high as the origin of the levator muscle from the white line of the pelvis. Since the white line is the usually accepted origin of the so-called fascia surrounding the vagina it seemed reasonable and anatomically correct to suture this perivaginal fascia to the white line and the underlying levator muscle with three interrupted sutures on each side. This maneuver produced a most satisfactory restoration of the normal anatomy of the bladder neck and, in addition, a surprising correction of most of the cystocele involving the base of the bladder. This demonstrated the possibilities of the operation not only in overcoming the anterior cystocele involving the neck of the bladder but also the posterior cystocele involving the base of the bladder.

Seven operations were performed with this technique. In all of these, an excellent anatomical result was obtained and the structures are holding well at this time. The white line, however, had the same disadvantage as the symphysis. It holds the sutures

poorly. The final step in the development of the operation to be described was the utilization of Cooper's ligament as a point of fixation. This strong thick band of fibrous tissue runs along the superior surface of the superior ramus of the pubic bone and is ideal from the standpoint of both passing and holding a suture. Cooper's ligament is well known to surgeons and is used as a point of fixation for the conjoined tendon in the repair of inguinal and femoral hernia and in the repair following a radical groin dissection. From the inguinal approach, Cooper's ligament seems to be a rather short structure but when viewed from within the abdomen, the structure is several inches long and affords more than enough room for the necessary sutures.

The present operation, like all operations, will probably not go too smoothly on the first few attempts but, once learned, it goes much better. In doing the operation, a few technical points may be of help. The dissection to expose Cooper's ligament and the fascia surrounding the vagina begins by breaking through the endoabdominal fascia, which descends from the anterior abdominal wall onto the symphysis and superior ramus of the pubic bone. The most convenient breakthrough site is at the lower angle of the abdominal wound and, when the fascia is broken through, the fingers rest on the bare bone of the symphysis. Now with the left index finger in the vagina and continuing in this plane, the endoabdominal fascia is stripped from Cooper's ligament and the side wall of the pelvis by the right hand. This plane is relatively avascular and keeping in it avoids the rupture of many small vessels and prevents a most troublesome ooze. In working downward to the fascia surrounding the vagina, the right hand sweeps the endoabdominal fascia from the lateral structures with a lateral and superior motion.

When the lateral edge of the vagina becomes apparent, further medial dissection will usually outline to some degree the edge of the bladder. The distinctness of the bladder edge is not always sharp, especially in the obese, and in passing the suture into the perivaginal fascia, one can easily penetrate the bladder. An excellent procedure used by surgeons for many years and resurrected by Dr. Charles Hobdy, is the instillation of 30 to 60 c.c. of sterile milk into the bladder through a previously inserted Foley catheter. If the milk is instilled at the start of the operation, however, the bladder becomes full and this fullness will interfere with the dissection. For this reason, the milk should be instilled just prior to making the dissection into the space of Retzius. Now if the milk-containing bladder is perforated by a needle, a drop of milk will immediately notify the operator of his mistake before further damage occurs.

For suture material, No. 2 chromic catgut has so far proved satisfactory. Perhaps stainless steel wire or even fascia may be the eventual choice. The point on the vagina through which the needle and suture have been passed is now matched to Cooper's ligament and the needle is passed through this ligament and tied by the assistant as the operator pushes up with the intravaginal finger (Fig. 1). Three such sutures are passed on each side (Fig. 2).

The abdomen is closed, the legs retracted, and perineorrhaphy and posterior colporrhaphy done if indicated. In case of doubt, it is best to repair the posterior vaginal wall. Special attention should be directed to it because many times it is noted that there is a submucosal band high and just in front of the cervix. Also, this part of the vagina has been elevated in the pelvis as a result of the suspension of the vagina and this changes the slope of the posterior wall so that it is more parallel to the plane of the operating table. Experience has shown that these changes predispose to the development of enterocele unless the cul-de-sac is obliterated. Attention to this point is important and may prevent a bad result.

When hysterectomy is necessary, as in the case of a large abdominal tumor, it may be advisable to perform the hysterectomy before the urethrovesical suspension. This order of procedure has been the usual one

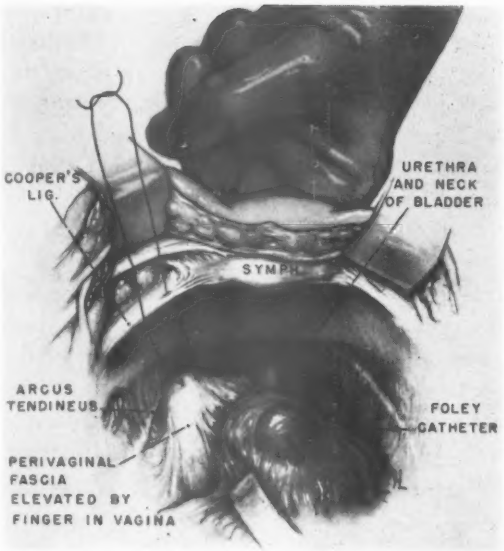


Fig. 1. The suture has been passed through the perivaginal fascia and the wall of the vagina, but not through the mucous membrane. The sutured point is now matched to that point on Cooper's ligament to which it is most easily approximated, and the suture passed through this point and tied.

in the cases reported; however, the order has been reversed at times and either order can be used at the discretion of the operator. After the abdominal closure, perineorraphy and posterior colporraphy are performed when indicated.

Case material

So far 53 patients have been subjected to the operation. The first operation was performed in May, 1958, and the follow-up period ranges from 2 to 17 months. Of the 53 operations, 40 were done by the author and 13 by Dr. Charles Hobdy or by other members of the staff with Dr. Hobdy's assistance.

The age range of the patients according to decades is shown in Table I. It is not surprising that 35 of the 53 patients were between 30 and 49 years of age.

The obstetrical background of the patient as regards parity is listed in Table II. It is interesting that 2 of the patients were nulliparas. The greatest number of patients were para ii and the next greatest number were para iii.

Table III considers the duration of symptoms. In more than half (28 of 53), the symptoms were of relatively short duration (between 0 and 2 years).

Symptoms of pelvic insecurity were present in 45 patients and lacking in 8 patients. The severity of these symptoms is noted in Table IV.

Stress incontinence occurred in 45 of the 53 patients. In 8 cases there was no stress incontinence, the operation being performed to correct a cystocele. In my hands urethro-

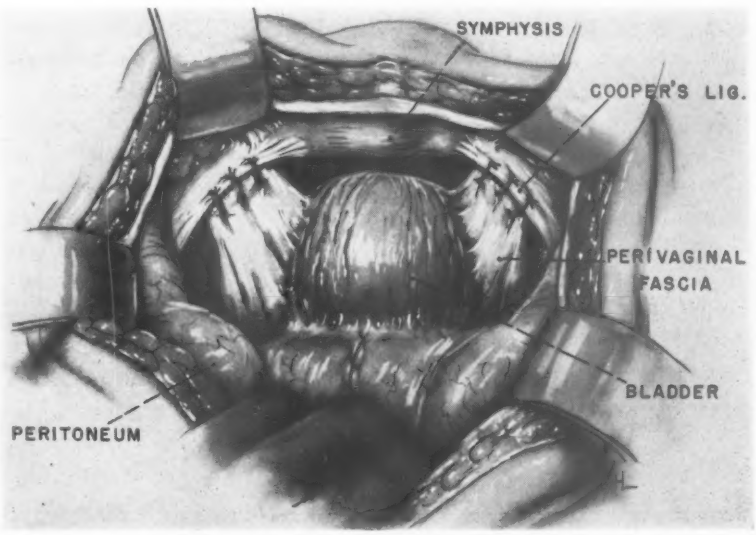


Fig. 2. The lateral edges of the vagina have been approximated to Cooper's ligament by 3 interrupted sutures.

Table I. Age range of patients at the time of operation

Age in years	*No. patients*
20-29	1
30-39	15
40-49	20
50-59	7
60-69	8
70-79	2

Table II. Obstetric background of patients

Para	*No. patients*
0	2
1	5
2	17
3	9
4	13
5	2
6	3
Unknown	2

Table III. Duration of symptoms

No. years	*No. patients*
0-2	28
2-4	12
5-7	7
9-10	2
Over 10	4

Table IV. Symptoms of pelvic insecurity found in total number of patients

Degree	*No. patients*
Mild	6
Moderate	31
Severe	8
None	8

Table V. Incidence and degree of stress incontinence

Degree	*No. patients*
Mild	20
Moderate	19
Severe	6
None	8

vesical suspension has so far achieved results as good as or better than the conventional operations for cystocele. It has a decided advantage, as no mucous membrane is removed and in those cases where it is necessary to insure a functioning vagina in the aged it is my present procedure of choice. Table V lists the stress incontinence according to degree of severity.

Table VI notes the degree of cystocele and rectocele. Unfortunately, it has not been possible to give any statistical evaluation of the prolapse of the uterus from a study of the records, as the descriptions of the degree of uterine descent were lacking in accuracy. Suffice it to say that the majority of the patients did exhibit good evidence of an unclassified prolapse and that 3 of the cases were clearly of third degree or complete prolapse.

In the treatment of stress incontinence the Marshall-Marchetti operation produces a favorable effect on the accompanying cystocele. Goetsch[4] has commented upon this, and Durfee[5] has recently elaborated on this in a most impressive manner. In my opinion, the Cooper's ligament urethrovesical suspension achieves an even greater degree of cystocele correction as fixation is from a firmer structure and the points of fixation are higher, more lateral, and posterior. Because of these advantages, I have used the Cooper's ligament anterior vaginal wall suspension to correct the anterior vaginal wall component of patients exhibiting cystocele, prolapse, cul-de-sac weakness, rectocele, and relaxed vaginal outlet. Hysterectomy is, of course, usually necessary in such cases, and in order to strengthen and tighten the upper supports of the vagina I devised a special method of suturing the cardinal and uterosacral ligaments. This was most effective as far as the supports of the vagina were concerned but it was faulty because it raised the posterior vagina in the pelvis and so deepened the already weakened cul-de-sac. In the later cases a modification of the Moschcowitz[6] operation was used to obliterate and strengthen the cul-de-sac (Fig. 3). This can be further improved when reperitonizing the pelvis by

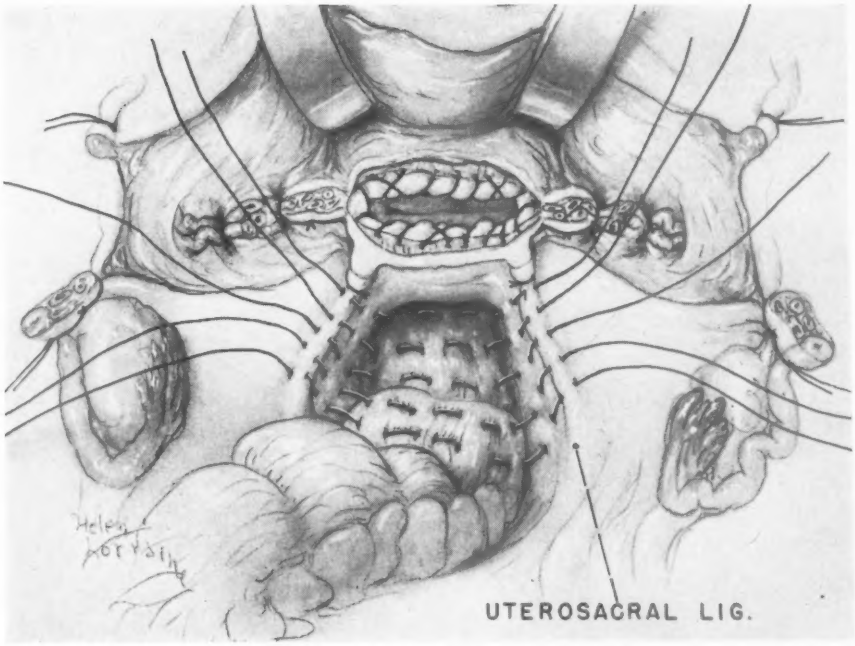


Fig. 3. Placement of the sutures for the obliteration of the cul-de-sac of Douglas. In placing the sutures it is easier to start posteriorly and proceed anteriorly as traction on the posterior sutures pulls up the structures and facilitates the passage of the next lowermost suture. Extreme care must be taken to avoid the ureter on the lateral walls of the cul-de-sac.

suturing the sigmoid colon to the anterior leaf of peritoneum and obliterating the right parasigmoid "gutter" with a few interrupted sutures (Fig. 4).

In Table VII it is seen that 15 of the 53 patients had undergone previous gynecologic operations. Four patients had had a previous unsuccessful operation for stress incontinence. The removal of the anterior wall redundancy in the conventional repair of cystocele and stress incontinence makes both the Marshall-Marchetti and the Cooper's ligament urethrovesical suspension more difficult. Considering the more difficult nature of a second operation, the uncertainty of cure for major stress incontinence by conventional means, the distressing condition of these patients, and the high curability of the anterior vaginal wall suspension operations, it is clear that these operations deserve more consideration for the primary attempt rather than being reserved for failures. A detailed list of the various gynecologic procedures previously performed on the patients is noted in Table VII.

Table VI. Degrees of relaxation found on examination

Cystocele		*Rectocele*	
Degree	*No. patients*	*Degree*	*No. patients*
1	10	1	11
2	37	2	24
3	6	3	7

Table VIII itemizes the various operations utilized. The anterior vaginal wall suspension operations correct the downward, outward, and upward displacement of the urethrovesical area, which is the common deformity seen in stress incontinence, by pulling this area inward and upward behind the symphysis. This reduction of the deformity we have described as "recession." In 7 cases the white line of the pelvis served as the point of fixation, while in 46 cases Cooper's liga-

Table I. Age range of patients at the time of operation

Age in years	*No. patients*
20-29	1
30-39	15
40-49	20
50-59	7
60-69	8
70-79	2

Table II. Obstetric background of patients

Para	*No. patients*
0	2
1	5
2	17
3	9
4	13
5	2
6	3
Unknown	2

Table III. Duration of symptoms

No. years	*No. patients*
0-2	28
2-4	12
5-7	7
9-10	2
Over 10	4

Table IV. Symptoms of pelvic insecurity found in total number of patients

Degree	*No. patients*
Mild	6
Moderate	31
Severe	8
None	8

Table V. Incidence and degree of stress incontinence

Degree	*No. patients*
Mild	20
Moderate	19
Severe	6
None	8

vesical suspension has so far achieved results as good as or better than the conventional operations for cystocele. It has a decided advantage, as no mucous membrane is removed and in those cases where it is necessary to insure a functioning vagina in the aged it is my present procedure of choice. Table V lists the stress incontinence according to degree of severity.

Table VI notes the degree of cystocele and rectocele. Unfortunately, it has not been possible to give any statistical evaluation of the prolapse of the uterus from a study of the records, as the descriptions of the degree of uterine descent were lacking in accuracy. Suffice it to say that the majority of the patients did exhibit good evidence of an unclassified prolapse and that 3 of the cases were clearly of third degree or complete prolapse.

In the treatment of stress incontinence the Marshall-Marchetti operation produces a favorable effect on the accompanying cystocele. Goetsch[4] has commented upon this, and Durfee[5] has recently elaborated on this in a most impressive manner. In my opinion, the Cooper's ligament urethrovesical suspension achieves an even greater degree of cystocele correction as fixation is from a firmer structure and the points of fixation are higher, more lateral, and posterior. Because of these advantages, I have used the Cooper's ligament anterior vaginal wall suspension to correct the anterior vaginal wall component of patients exhibiting cystocele, prolapse, cul-de-sac weakness, rectocele, and relaxed vaginal outlet. Hysterectomy is, of course, usually necessary in such cases, and in order to strengthen and tighten the upper supports of the vagina I devised a special method of suturing the cardinal and uterosacral ligaments. This was most effective as far as the supports of the vagina were concerned but it was faulty because it raised the posterior vagina in the pelvis and so deepened the already weakened cul-de-sac. In the later cases a modification of the Moschcowitz[6] operation was used to obliterate and strengthen the cul-de-sac (Fig. 3). This can be further improved when reperitonizing the pelvis by

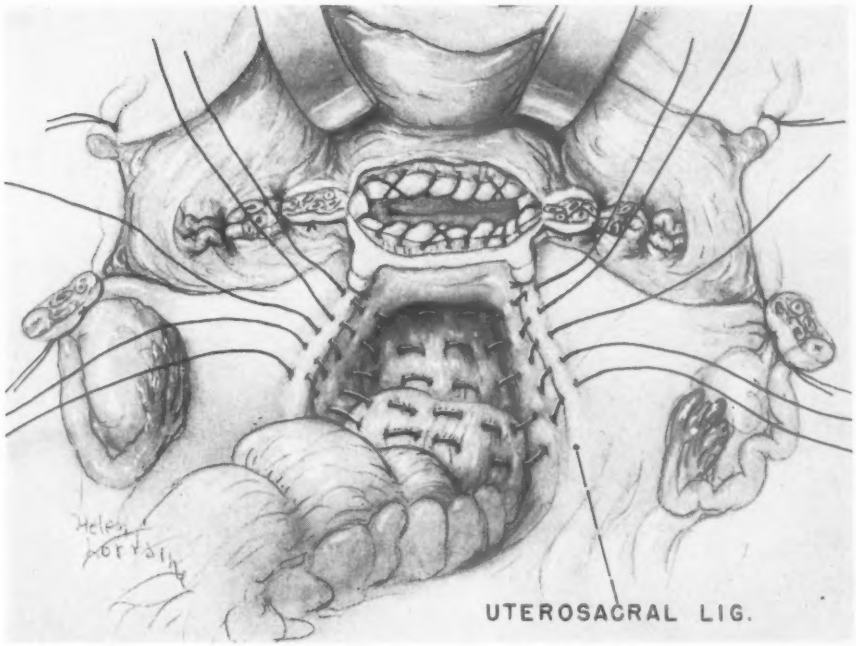


Fig. 3. Placement of the sutures for the obliteration of the cul-de-sac of Douglas. In placing the sutures it is easier to start posteriorly and proceed anteriorly as traction on the posterior sutures pulls up the structures and facilitates the passage of the next lowermost suture. Extreme care must be taken to avoid the ureter on the lateral walls of the cul-de-sac.

suturing the sigmoid colon to the anterior leaf of peritoneum and obliterating the right parasigmoid "gutter" with a few interrupted sutures (Fig. 4).

In Table VII it is seen that 15 of the 53 patients had undergone previous gynecologic operations. Four patients had had a previous unsuccessful operation for stress incontinence. The removal of the anterior wall redundancy in the conventional repair of cystocele and stress incontinence makes both the Marshall-Marchetti and the Cooper's ligament urethrovesical suspension more difficult. Considering the more difficult nature of a second operation, the uncertainty of cure for major stress incontinence by conventional means, the distressing condition of these patients, and the high curability of the anterior vaginal wall suspension operations, it is clear that these operations deserve more consideration for the primary attempt rather than being reserved for failures. A detailed list of the various gynecologic procedures previously performed on the patients is noted in Table VII.

Table VIII itemizes the various operations utilized. The anterior vaginal wall suspension operations correct the downward, outward, and upward displacement of the urethrovesical area, which is the common deformity seen in stress incontinence, by pulling this area inward and upward behind the symphysis. This reduction of the deformity we have described as "recession." In 7 cases the white line of the pelvis served as the point of fixation, while in 46 cases Cooper's liga-

Table VI. Degrees of relaxation found on examination

Cystocele		*Rectocele*	
Degree	*No. patients*	*Degree*	*No. patients*
1	10	1	11
2	37	2	24
3	6	3	7

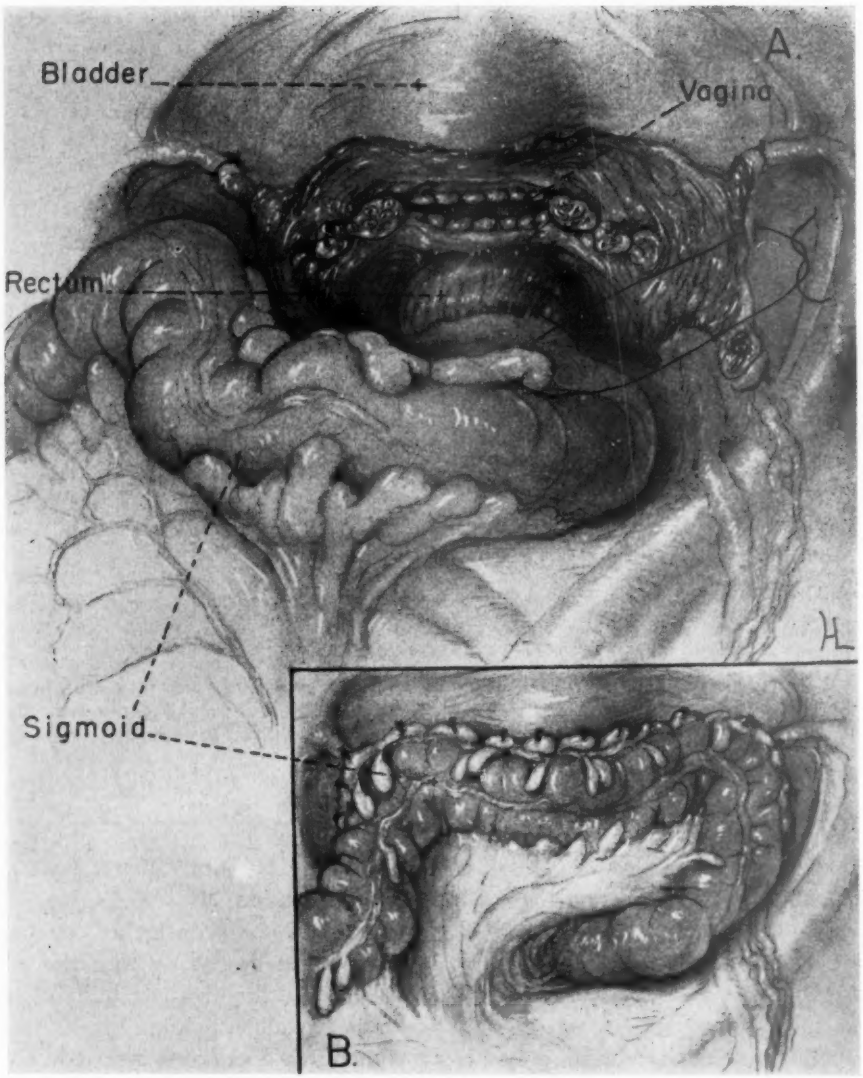


Fig. 4. The pelvis is further obliterated when the sigmoid colon is sewn to the anterior or vesical leaf of the peritoneal defect. A few additional stitches are necessary to obliterate the right parasigmoid gutter. (From *Hysterectomy* by John C. Burch and Horace T. Lavely, Springfield, Ill., 1954, Charles C Thomas, Publisher.)

ment was used. In only one of our cases was any operation done from the vagina on the anterior vaginal wall. This was one of the early cases and a simple anterior wall repair of the Graves' type was employed on the posterior part of a large cystocele. A posterior wall repair was done whenever necessary and this was in 45 cases. Hysterectomy was done in 36 cases—one vaginal and 35 abdominal. The uterus was suspended 5 times. In the remainder of the cases no uterine operation seemed indicated. The plication of the uterosacral and cardinal ligaments to elevate and fix the upper end was done in 10 cases. This procedure was not satisfactory and was abandoned in favor of the Moschcowitz type of cul-de-sac obliteration, which was used in 5 cases.

Results

The results of the operations are itemized in Table IX. A satisfactory correction of the

anterior vaginal wall was initially obtained in every case. So far, this has been maintained. In the immediate postoperative period the anterior wall seems to be markedly overcorrected, but as time goes on it assumes a more normal contour. In one case of total prolapse there is a sagging of the posterior portion of the cystocele but this is well supported by the perineum and the patient is asymptomatic. In the 45 cases of stress incontinence there have been no failures. In one case of total eversion of the vagina following an abdominal hysterectomy, mild stress incontinence persisted for 3 months. The operation was performed in another hospital by an excellent surgeon and consisted of a Cooper's ligament urethrovesical suspension and Brady fixation of the top of the vagina to the anterior abdominal wall. When the catheter is first removed, many of the patients have difficulty in voiding, the degree is about the same as with the Marshall-Marchetti or the sling operation. Either immediately or following the period of urinary retention there is a period in which urge incontinence may occur but with subsidence of urinary infection this vanishes. However, some of the patients continue to complain of mild urinary discomfort from time to time. This is not serious and probably represents about the same number as in the general population.



Fig. 5. Cystourethrograms with patient in standing anteroposterior position. *A*, Preoperative. *B*, Postoperative. *C*, Preoperative-straining. *D*, Postoperative-straining.



Fig. 6. Cystourethrograms with patient in standing lateral position. *A*, Preoperative. *B*, Postoperative. The notch on the floor of the bladder is posterior to the urethrovesical junction and is of no adverse clinical importance. *C*, Preoperative—straining. *D*, Postoperative—straining.

Postoperative cystograms reveal the remarkable degree of correction obtained by the operation (Figs. 5 and 6). In Fig. 6, a lateral view, a notch is seen on the posterior or vaginal surface of the bladder. Our urologic consultants report that this is consid-

erably less prominent on cystoscopic examination. Certainly it has not assumed any great clinical importance or been associated with permanent residual urine of a significant degree.

Enterocele has been the chief complication, occurring in 4 instances. Three of these followed a total abdominal hysterectomy and plication of the cardinal and uterosacral ligaments, while one case occurred after the uterus was suspended by the Olshausen technique. In each instance the depth of the cul-de-sac was increased by the operative procedure, and this allowed a greater degree of intra-abdominal pressure to be exerted on an already large and weakened cul-de-sac. Since abandoning the plication of the cardinal and uterosacral ligaments and utilizing the Moschcowitz type of procedure the postoperative results have been much better and I do not believe that the development of postoperative enterocele will be a major problem in the future. The postoperative condition of the cul-de-sac following the Moschcowitz procedure is remarkably similar to that obtained by the McCall[7] vaginal type of cul-de-plasty.

The vesicovaginal fistula occurred in one of the early cases and was a complication of the hysterectomy and not of the urethrovesical suspension. It was the first such complication in a series of more than 2,000 cases.

Table VII. Previous pelvic surgical procedures

No. patients	15
No. patients that had surgical procedures for stress incontinence	4
Pelvic procedures performed	
Curettage	6
Hysterectomy	5
Extrafascial hysterectomy	1
Vaginal plastics	4
Bilateral salpingo-oophorectomy	1
Oophorectomy	1
Tubal ligation	1
Salpingectomy	2

Table VIII. Surgical procedures performed

Urethral recession		53
White line	7	
Cooper's ligament	46	
Anterior colporrhaphy (Graves')		3
Posterior colporrhaphy		45
Perineorrhaphy		45
Total abdominal hysterectomy		35
Total vaginal hysterectomy		1
Curettage		9
Bilateral salpingo-oophorectomy		16
Plication of uterosacral and cardinal ligaments		10
Appendectomy		27
Marsupialization of Bartholin gland cyst		1
Brady procedure		1
Repair of umbilical hernia		1
Moschcowitz's operation		5
Uterine suspension (Olshausen)		5
Excision of breast tumor		1

Table IX. Results of 53 cases

Fixation of anterior vaginal wall in anatomic position with urethral recession	53
Failure to relieve stress incontinence	0
Postoperative complications	
Recurrence of rectocele and enterocele	4
Ventral hernia	1
Vesicovaginal fistula	1

Conclusions

Experience with Cooper's ligament urethrovaginal suspension indicates that it is a superior operation for urinary stress incontinence. It achieves a remarkable degree of correction of the deformity of cystocele and gives for the first time a satisfactory correction of almost all types of cystocele by the abdominal approach.

It can be combined with abdominal hysterectomy and perineorraphy in the treatment of uterine prolapse, but in these cases the danger of the subsequent development of enterocele must be recognized and appropriate precautions taken.

The operation also produces excellent results following failures of the usually employed operations for stress incontinence provided there is enough redundancy in the the anterior vaginal wall to allow approximation to Cooper's ligament.

In those cases of cystocele, stress incontinence, or prolapse in the aged in which it is necessary to maintain a functioning vagina it is a worthwhile and useful procedure.

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Culdoplastic technique for prevention and correction of vaginal vault prolapse and enterocele

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PELVIC relaxations are among the most symptom-producing pelvic troubles in parous women. They maintain their peculiar interest because of the persisting problem of correction, attested by the seemingly unlimited and varied surgical procedures employed. Some of these are good, some are not. The most commonly employed and successful operations are the Manchester-Fothergill, in which the uterus is retained, and vaginal hysterectomy, in which it is removed. These are accompanied by repair of existing cystocele, urethrocele, rectocele, enterocele, and perineal relaxation. If the operation is done well, the results with either one are generally good, for the basic principles utilized in restoration are anatomically sound. A serious complication is an unpredictable and high incidence of enterocele with vaginal vault prolapse subsequent to vaginal operation. This was mentioned by Ward[1] 37 years ago.

The first important suggestion for the cure of enterocele was by Marion[2] in 1909, who proposed transabdominal obliteration of the cul-de-sac with purse-string sutures of nonabsorbable material. This technique was slightly modified and used by Moschcowitz[3] 3 years later for prolapse of the rectum. A well-studied vaginal approach and technique was presented by Ward[1] in 1922, who used sound anatomic principles derived from investigations in his clinic.

Additional technical steps have been suggested by Torpin,[4] Counsellor,[5] Shaw, Hiller,[6] Waters,[7] McCall,[8] and others. Phaneuf[9, 10] and Read[11] published follow-up studies of patients treated by differing techniques with recurrences of nearly 10 per cent following the vaginal surgical approach. Most of Read's cases of enterocele repair were with Manchester-Fothergill operations, while American reports largely concern vaginal hysterectomies. The literature intimates that some poor results are invariable sequelae of usual procedures.

A poor end result can be anticipated if at operation the uterosacral attachments are widely separated, the vaginal vault yawning, the cul-de-sac deep, or a definite enterocele present. A common cause of failure after vaginal hysterectomy is the persistence of an unrecognized enterocele which develops rapidly through the surgically weakened endopelvic fascia. This diagnostic omission is needless, for enterocele with or without rectocele positively can be diagnosed preoperatively. The simple and rapid technique which we described and published[12] in 1946 is unfailing. Postoperatively, a developing enterocele will pull the vaginal vault down during its evolution. Most often overlooked, however, is the smaller enterocele which tends to flatten out and "disappear" after vaginal hysterectomy when traction is exerted upon the posterior vaginal cuff. These

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operative failures with recurrence are usually discernible within a few months and almost invariably within the first year after operation.

We have described and reported[13] a procedure designed to prevent postoperative vault prolapse or enterocele development. This is applied in conjunction with vaginal hysterectomy or used to supplement a Manchester operation. It is also suitable when reoperating on patients who have developed vaginal herniations subsequent to other abdominal or vaginal operations. The basic needs satisfied by this culdoplastic technique

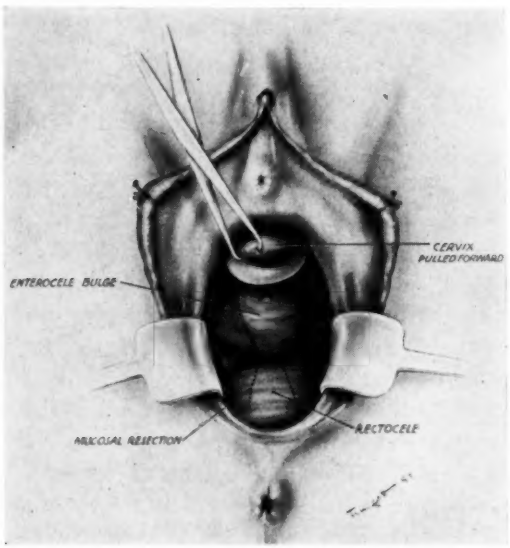


Fig. 1. Enterocele and rectocele relationship shown with cervix held forward. Area of vaginal wall excised in radical correction is outlined.

are (1) an excision of a wedge-shaped section of upper posterior vagina with the base between the uterosacral ligaments, (2) excision of the redundant peritoneum of the cul-de-sac, (3) approximation of the uterosacral ligaments, and (4) narrowing of the vaginal vault. The direction of vaginal vault support given by the uterosacral ligaments when the erect posture is assumed has been a matter of anthropologic interest and has been well recorded by Davies.[14] Our technique borrows from this knowledge as it utilizes the long-recognized worth of these structures as means for closing this pelvic hiatus. Where vaginal redundancy is notable as in many multiparas, a partial posterior colpectomy is performed in addition to repair of the enterocele and posterior vault wedge resection. Success is measured by attaining (1) narrowing of the caliber of the vaginal vault, thus precluding vaginal inversion, (2) obliteration of the enterocele or enterocele site, preventing recurrence with induced vault prolapse, (3) excision of the hernial sac, (4) narrowing the entire vagina where it has been notably redundant, and (5) actual deepening of the vagina.

Technique of procedure

The technique used to accomplish these essentials is detailed as follows: The uterus is removed vaginally and (Fig. 2) the peritoneum closed with a purse-string of 0 chromic suture. The first stitch is placed high on the bladder, then the anterior peritoneum of the broad ligament, the round ligament, adnexa, and posterior peritoneum of the broad ligament. Reaching high on the sigmoid, a good bite is taken in the longitudinal muscle band. It is then continued in like manner (reverse order) around the left side, back to the bladder and the structures drawn together and the suture tied. This produces a very high peritonization with exclusion of the vascular pedicles, as well as the cul-de-sac and/or enterocele. The redundant cul-de-sac peritoneum or enterocele sac below the suture line is now dissected and excised. This may be done by finger or scissor dissection and, while not extensive, should be complete. To insure a cure, we believe, the sac must be removed as with any hernia.

The new vaginal vault is constructed by passing sutures through the lateral vaginal walls and the cardinal ligaments about one inch posterior to the site of the cervix, thus securing a longer anterior vaginal wall. Another suture passes through the lateral vaginal walls and the uterosacral ligaments, emerging about a quarter inch on each side of the cut mucosa. These 2 sutures will firmly fix the vaginal vault to the supporting

ligaments but *are not tied* until the subsequent steps are completed. The cystourethropexy is next done. Then a broad triangular wedge of the upper posterior vaginal wall is excised (Fig. 3). Its base is in the posterior fornix, the uterosacral ties being its extremities, while the apex is above the top of the rectocele bulge. This is accomplished in the following manner (Fig. 4):

A scissor dissection is carried upward from the perineum behind the full thickness of the posterior vaginal wall, emerging at the upper edge of the open vaginal vault between the vaginal wall anteriorly and the rectum posteriorly. The freed posterior vagina is now divided in the midline halfway to the new vault, where the incision is extended off to the right and then left as a "Y," ending at the uterosacral ties, thereby removing a triangular or wedge-shaped area of the upper posterior vaginal wall. Tension on the uterosacral ties gathers and exposes the uterosacral ligaments which are now secured firmly with 2 sutures, thus approximating the ligaments and the vaginal walls at the base of the wedge. By tying these and then drawing together the 2 loose sutures previously placed in the vault, the pubocervical, cardinal, and uterosacral ligaments are firmly bonded at the vault, with the uterosacral approximation completely closing off the enterocele site. Excess vaginal mucosa is now removed and a continuous fine 3-0 chromic suture is placed from the vault to the level of the rectocele. Partial posterior colpectomy is done from wedge to perineum where vaginal laxity warrants. Adequate perineal repair now completes the task. It will then be noted that the closing suture line runs in continuity from the urethra anteriorly to the vault and then down posteriorly to the perinuem. There has been produced a vaginal of adequate size with a narrowed vault, having a cone effect. The entire vagina is deepened with complete extirpation of the cul-de-sac peritoneum or enterocele through wedge-shaped excision.

There are some worthy points to be remembered in this procedure. First, after

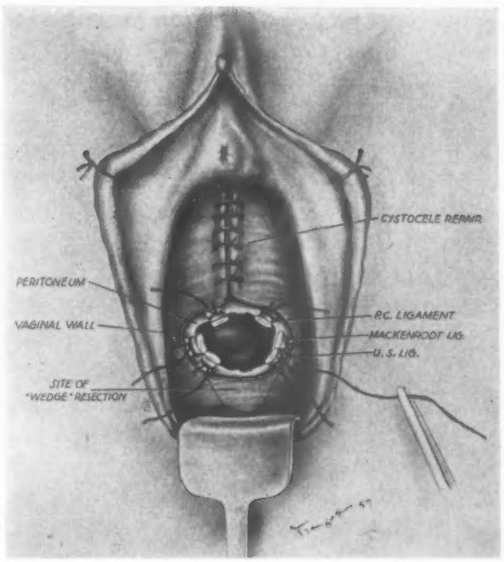


Fig. 2. Vaginal hysterectomy with high peritonization and cystocele repair have been completed. The site of wedge resection is outlined for lax upper vagina. High peritonization (not shown) of cul-de-sac excludes enterocele posterior to vaginal vault. Cardinal and uterosacral ligaments tagged with sutures.

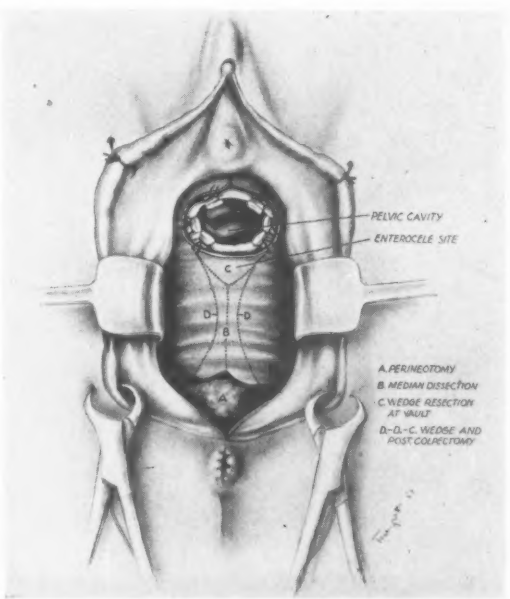


Fig. 3. Median perineotomy precedes vaginal hysterectomy. Following steps in Fig. 2, subvaginal dissection carried from perineotomy to vault opening, anterior to enterocele. Vault wedge resection *C* completed for average vagina. With lax vagina, area within *D* also removed (entire vaginal wall thickness).

peritonization, the vault must be left "open" and the 2 vault sutures held loosely and untied in order to visualize this area and properly place the uterosacral sutures. Next, it is well to identify the apex of the wedge or triangle to be resected with Allis or "T" clamps or sutures so that orientation is not lost after the wedge of posterior vault vagina has been excised. This is especially true if partial posterior colpectomy is an added step in the voluminous vagina. One also encounters the vaginal artery in the upper third of the vagina, usually near the apex of the wedge. This should be ligated to prevent postoperative hemorrhage. It is also most important to identify and bring together with sutures the fibroareolar condensations which form the uterosacral ligaments before tying the loose vault sutures. After closing the peritoneal cavity, any enterocele sac must be identified, dissected, and excised, a step consonant with all good hernia operations. We have found that the use of a hemostatic substance such as Adrenosem lessens bleeding and helps keep the field clean, facilitating the accomplishment of the entire procedure. Also, the vault should be narrowed to assure success. It is normally capacious because it must contain the cervix in parturition or at rest. The use of a vaginal gauze packing for 24 hours minimizes the possibility of subvaginal formation of hematomas. Intravaginal bacteriostatic medications improve the healing rate. A final word of some interest concerns the time required for this added technique. The operating time at most is lengthened by 10 minutes.

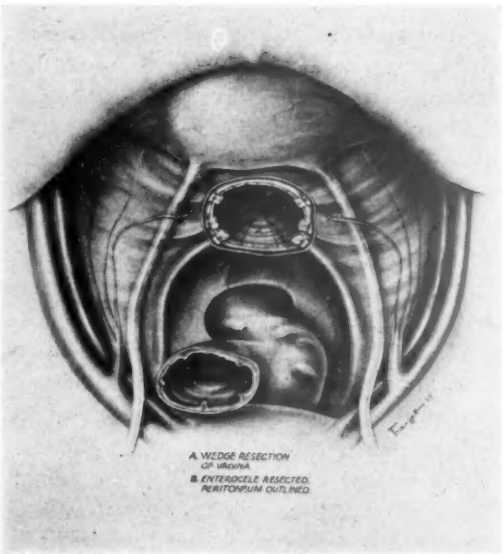


Fig. 5. Abdominal view. High peritonization *not shown*. After excision of enterocele sac and wedge of posterior vaginal wall, uterosacral ligaments are approximated to occlude cul-de-sac area. Vaginal repair is then completed.

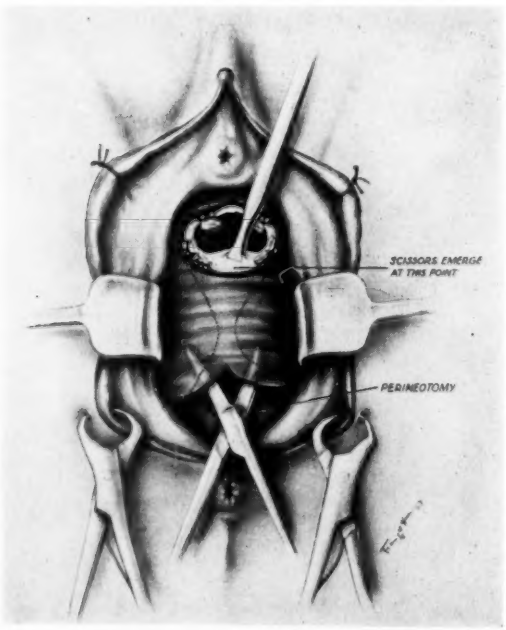


Fig. 4. Preparation for midvaginal incision *B*. Scissors emerge at vault between vagina and anterior edge of sac. Peritoneum of enterocele sac freed by finger and scissor dissection and excised. Vaginal wedge freed and excised. Uterosacral ligaments approximated distally with 2 sutures before joining stumps in midline. Extent of lower vaginal excision determined by laxity and coital needs.

Selection of material

The technique described has now been used in 115 cases. Seventy-two of these have been continuously re-examined for a minimum of 2 years. All are private patients and are under continuing observation.

Of the 72, the procedure was part of a vaginal hysterectomy and repair in 53 in-

stances. In 6 cases it was incorporated with an otherwise usual Manchester-Fothergill operation.

The past surgical history of these 72 cases records significant data. Three patients had vaginal plastic operations (without hysterectomy) for relaxation. Six had vaginal hysterectomies with vaginal plastic procedures. Five had supravaginal (abdominal) hysterectomies, and one a total abdominal hysterectomy. Thus, over 20 per cent of the entire group had previously undergone operation for the persisting or subsequent pathology.

Complications

Some complications were encountered shortly after the operation. Three patients had postoperative vaginal bleeding, one severe. In all instances this was due to failure to properly secure the superior vaginal artery. Two patients one of whom required rehospitalization for 5 days, had pelvic abscesses which drained spontaneously. No pelvic drains were placed in any of the patients.

Results

In the follow-up study ranging from 2 to 5 years, one patient had incontinence without recurrent cystocele. This was her second operation for prolapse and third operation to control incontinence. The anatomical result is good, but she still wets and another approach is now needed. There were no cases of complete incontinence. There was some stress incontinence in 3 patients, one of whom had no bladder repair done at the original operation. In the other 2, the stress incontinence is only occasional or inconstant. *In no instance* was there a vault prolapse or recurrence of enterocele, and this is the essential project of this technique.

These results contrast with those in a group of 210 vaginal hysterectomies with vaginal plastic operation in which this procedure was *not* used. There were 14 significant recurrences of cystocele, enterocele, and/or vault prolapse of varying degrees. This is approximately the failure rate reported by Phaneuf[15] in 1953 on 91 cases.

While 72 cases is not a large series, the opportunity for a careful follow-up study in these private patients presenting the results obtained is a strong indication of the value of the operation.

Summary

A culdoplastic technique is described for the correction of enterocele and prevention of postoperative enterocele and vaginal vault prolapse. It involves a relatively simple addition to vaginal hysterectomy or other vaginal operation for prolapse accompanied by enterocele of any degree. Attained in the procedure is high obliteration of the cul-de-sac, excision of the enterocele (hernial) sac, purposeful narrowing of the vaginal vault, narrowing of any redundant vagina, and increase in vaginal depth.

This operation has been used in 115 private patients, 72 of whom have been followed more than 2 years. A statistical contrast of results is given with 210 cases in which this procedure was *not* used. The reliability of the technique is indicated by the results, which have been consistently good.

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Discussion

Dr. E. Everett Bunzel, New York, New York. This is a very important subject, because we see this condition so frequently in our work.

There are two points that are of particular significance in what Dr. Waters has stated. The first is the importance of noting what has been done previously, and the second, what the exact anatomical conditions are.

Dr. John Glasser, New York, New York. I was with Dr. Waters for 3 years, during which time I learned to do this procedure. It is a very valuable addition to the technique of any vaginal hysterectomy.

The important point, I think, is to be sure an enterocele is present. Back in 1946 Dr. Waters gave a very simple method of diagnosing enterocele preoperatively. Most of us overlook enterocele. When we find one in the postoperative period we regard it as a recurrence.

I have used this operation in about 30 cases of my own, and I am very satisfied with it. It does take me a lot longer than 10 minutes.

There is one point I would like to add. After you have the uterus out, and as you are placing the purse-strong suture, you should pull the anterior rectal wall down and include a small bite of the serosa in the purse-string suture; then, insert the finger into the cul-de-sac and see how deep it is.

Some women have a much deeper cul-de-sac than others. Dr. Goff, Dr. Bissell, Dr. Ward, and many other eminent New York gynecologists have stressed this over the years. We should all profit by it. The woman with the long cul-de-sac is the one who is going to have a postoperative vault prolapse.

I think this method is much better than Torpin's, in which a Kelly clamp is placed on each side of this triangle of posterior vaginal wall and enterocele pouch. There may be a lot of bleeding from the pedicles. Dr. Water's method is easier and better. Actually, the principle is in Bonney's textbook, if you will take the trouble to dig it up.

Dr. Thomas L. Ball, New York, New York. In 1918, two brothers, both gynecologists in England, had their studies published on the anatomy and physiology of the female pelvic floor. These volumes are published by R. H. Paramore, F.R.C.S.(Eng.), his younger brother, Gordon, having fallen at Loos, Sept. 25, 1915. These two volumes are entitled *The Statics of the Female Pelvic Viscera.* A copy is available in the New York Academy of Medicine. The National Library of medicine in Washington has the volumes. I have been fortunate to acquire a set of these classics in our field.

The Paramore brothers describe what has very properly been referred to as the hiatus of the pelvic floor and its obturators. The obturators are the urethra, the vagina, and the rectum. The hiatus is created by the anatomical fact that the muscles of the pelvic floor, although paired, do not insert directly in the midline. The obturators must pass, or pathologically prolapse, through this hiatus or its dilated version seen with pelvic relaxation.

The authors completely discard the concept of ligaments to the pelvic organs. The uterosacral ligaments, the cardinal ligaments, and the round ligaments are discounted in terms of the classic description of a ligament. What we deal with in vaginal reconstructive operations is the visceral extensions of the parietal connective tissue. I believe, as does Dr. Waters, that we must think of the pelvic floor as a supporting structure composed of its several obturators through which they exit.

The technique that Dr. Waters described originally came to my attention in the American Journal of Obstetrics and Gynecology, Supplementary Volume 61A. This volume was, apparently, published in a limited edition since it is difficult to locate. In this volume is published an article by Dr. A. Watson, of New Zealand, read in 1951. He describes some hundreds of operations of this type and principle. When I talked to him personally during a visit to New York he said that his patients were frequently women who herded cattle and sheep, rode horseback, had large babies, and usually had a complete prolapse. He described this obliteration of the cul-de-sac much the same as Dr. Waters but with a more extensive dissection. To obliterate

the cul-de-sac you must dissect completely back to the hollow of the sacrum, denude the area of peritoneum, and then, in your reconstruction, close the tissues allowing only enough of a hiatus for the rectosigmoid. Watson's results were good considering that his patients would soon return to their previous arduous tasks.

I think we should all orient our thinking, as Dr. Waters has indicated, and cease talking about ligaments that don't exist in the true anatomical definition. We should stop hitching this ligament to that ligament in our descriptions of pelvic operations. It would be better to think in terms of obliterating or narrowing the hiatus through which the herniations occur. It would be better to think of the strengthening of the obturators by the repair on the anterior and posterior vaginal walls.

Why not consider plastic reconstruction of the pelvic floor as connective tissue extensions that accompany the blood vessels, the nerves, the lymphatics, and this parietal connective tissue as the supports we use. The so-called ligaments are actually only connective tissue extensions of the uterine, the middle hemorrhoidal, the vesical, and the vaginal nerves, vessels, and lymphatics. Dr. Waters has brought attention to anatomists of the female pelvic floor a realistic concept. It is hoped that more teachers will bring this concept to the attention of the surgeons they are training.

Dr. Waters (Closing). When we speak of pelvic ligaments or cervical ligaments we all know what it is we are talking about. We all know that there is no fascia in the sense of a canvas sheet that runs down from the cervix. We know that what we used to call the fascia is the outer half of the vaginal wall, which some of us have carefully split and ruined in trying to fix cystoceles. When we talk about ligaments, I think we all know the term is a convenient way of referring to condensations and muscular thickenings and condensations in and along existent pelvic structures.

I certainly do not agree, however, that the tough fascial structures that we encounter represent simply the continuations of the pelvic fascial components, with the blood vessels of the pelvis. I think I can demonstrate that the ligamentous structures to which we give some of these old names, or new names, actually do exist. They are distinct and separate from such structures as the uterine arteries.

OBSTETRICS

Uteroabdominal pregnancy

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UTEROABDOMINAL pregnancy is defined as a form of ectopic pregnancy where a portion of the fetus is outside of the uterus and a portion in the uterine cavity—or a fistulous communication between the fetal membranes and endometrial cavity which would permit the passage of amniotic fluid or fetal appendages.

Etiology

The cause may be (1) attempted criminal abortion; (2) defective scar, either from cesarean section or salpingectomy; (3) angular implantation of ovum; (4) implantation of ovum in a stump of a tube.

Case reports

A. Artificial passage created by an attempted criminal abortion. This 25-year-old woman, gravida i, whose last normal menstrual period was Sept. 18, 1946, had an attempted criminal abortion in November, 1946. She was admitted to our service Dec. 23, 1946, with a diagnosis of suspected ectopic pregnancy, but signed herself out of the hospital against medical advice. She was readmitted May 10, 1947, with a diagnosis of fetal death in utero. Pelvic examination at this time revealed a thick, closed cervix. The uterus was enlarged to a size consistent with a 3 months' gestation and was pushed downward and backward. Above the uterus anteriorly was a tender cystic mass which extended to a level 3 cm. above the umbilicus. A diagnosis of possible abdominal pregnancy was made.

At operation there was a large cystic mass anterior to the uterus. In this cystic mass was a dead fetus of approximately 5 months' gestation. The sac containing the fetus communicated with the endometrial cavity through a fistulous opening 4 cm. in diameter. A subtotal hysterectomy and right salpingo-oophorectomy were performed. The patient had an uneventful postoperative course.

B. Suspected attempted criminal abortion. This 29-year-old woman, gravida iii, para ii, whose last normal menstrual period was Nov. 15, 1955, was first seen in May, 1956. Abdominal examination revealed the fetus to be in a transverse presentation with a heart rate of 140. The patient was treated for pyelitis in June. After this no fetal movements were felt, no fetal heart sounds were heard, and x-ray confirmed the diagnosis of fetal death in utero. The patient failed to go into labor spontaneously and failed to respond to medical induction.

She was taken to the operating room Sept. 17, 1956. Just beneath the peritoneum was a purplish mass, believed to be necrotic myometrium. This necrotic tissue was bluntly separated from the peritoneum. Inadvertently the mass was ruptured, releasing foul amniotic fluid and a dead

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fetus. The necrotic tissue encasing the fetus and placenta communicated with the endometrial cavity through a fistulous opening 5 cm. in diameter in the posterior surface of the fundus. The necrotic myometrium was removed and the opening into the uterus was closed. The patient had a relatively uneventful recovery.

C. Suspected attempted criminal abortion. This 31-year-old woman, gravida iii, para ii, whose last normal menstrual period was Nov. 23, 1957, was admitted to our service Jan. 30, 1958, with a diagnosis of threatened abortion. She improved and was discharged to a private physician Feb. 6, 1958. She was readmitted in active labor Aug. 25, 1958. Abdominal examination revealed the baby to be in a left sacroanterior position. The fetal heart rate was 144 and the rhythm regular. Sterile vaginal examination revealed the cervix to be 30 per cent effaced and 4 cm. dilated. The membranes were intact and the presenting part (breech) was at station minus 4. Asymmetry of the uterus during contractions was noted which gave the impression of 2 masses. There was a regularly contracting mass anteriorly, and a posterior portion which seemed to contract irregularly. The clinical impression was bicornuate uterus. After spontaneous rupture of the membranes the cervix remained 30 per cent effaced and 4 cm. dilated. In view of the prolonged ineffective labor and unusual asymmetry of the uterus during contractions a cesarean section was performed.

A transverse incision was made into the lower uterine segment and a viable 7 pound, 15 ounce female infant was delivered. Exploration of the endometrial cavity for the placenta disclosed that it was located in a pseudo-sac posterior to the uterus, communicating with the endometrial cavity in the lower uterine segment by a fistulous tract 10 cm. in diameter. This sac was composed of the posterior portion of the broad ligament, the left ovary, the left tube, rectum, and sigmoid (Fig. 1).

A subtotal hysterectomy with removal of the placenta and portion of the sac and left salpingo-oophorectomy was performed. The postoperative course was uneventful except for a mild amount of ileus and an episode of diarrhea.

D. Defective scar from cesarean section. This 27-year-old woman, gravida iv, para ii, who

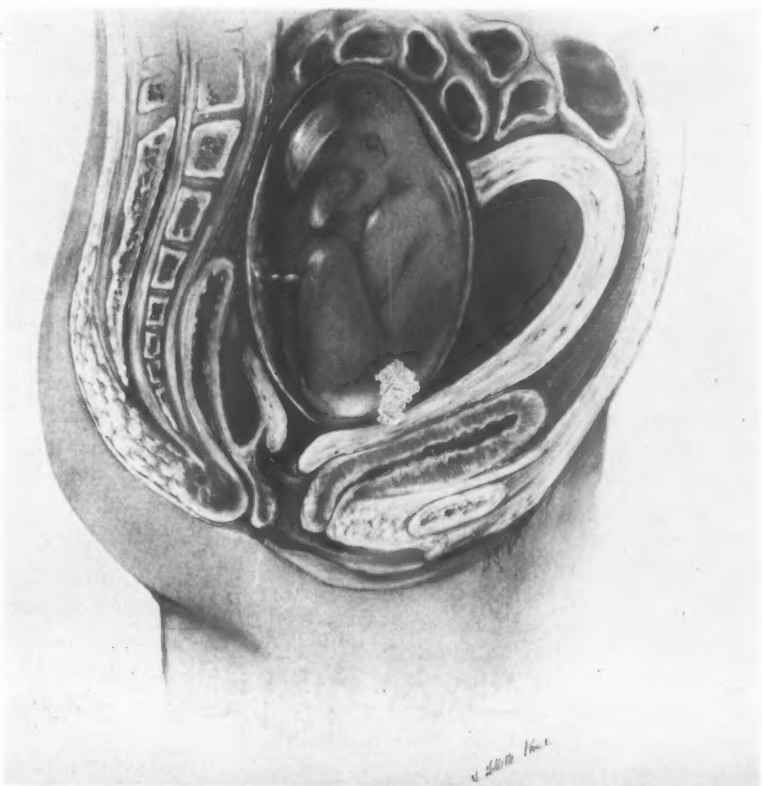


Fig. 1. Case 3. Example of uteroabdominal pregnancy.

had had one cesarean section and whose last normal menstrual period was Sept. 27, 1950, was seen Dec. 28, 1950, with a history of amenorrhea in October and hypomenorrhea in November and December. Significant past history included a classical cesarean section Nov. 24, 1949, for placenta previa.

Bimanual examination revealed a mass in the right lower quadrant 7 to 8 cm. in diameter and a second mass arising out of the pelvis on the left and extending to a level 5 cm. above the umbilicus. The impression at this time was intrauterine pregnancy and left ovarian cyst. The patient did not return again until April 12, 1951, when she was admitted complaining of vague right lower quadrant pain and history of genital spotting. The abdomen at this time was enlarged to a size consistent with a 6½ months' pregnancy. Bimanual examination revealed 2 masses; one consistent with a 6½ months' gestation and one in the right lower quadrant the size of a 4 months' pregnancy. X-ray for abdominal pregnancy was reported as showing intrauterine pregnancy. Symptoms did not persist and the patient was discharged to the clinic where she was followed. She was readmitted May 21, 1951, with a history of genital bleeding and suprapubic pain. The patient was noted to have moderately hard uterine contractions 6 minutes apart. There was severe midline suprapubic tenderness. A diagnosis of impending uterine rupture was made and the patient prepared for surgery.

When the peritoneum was opened the fetal head was found to be outside the uterus. A stillborn nonmacerated full-term infant was delivered. The uterus was found to be open on its anterior surface from the fundus to a point several centimeters above the internal os. The midportion of the opened uterine scar contained a mound of decidual tissue. The edges of the superior 5 cm. of the uterine opening appeared to be fresh, suggesting a recent rent. The inferior edges of the opening were overgrown by decidual tissue. The placenta was found free in the right lower quadrant of the abdomen, and a careful search for a site of attachment failed to show any place other than the mound of decidual tissue previously mentioned. There was no free blood found when the peritoneum was opened, but bleeding became profuse and uncontrollable during the procedure. A subtotal hysterectomy was performed. The patient had an uneventful postoperative course and was discharged on the tenth postoperative day.

E. Angular implantation of ovum. This 34-year-old woman, gravida iii, para i, who had had 1 tubal pregnancy and whose last normal menstrual period was April 21, 1956, was admitted to our service Dec. 1, 1956, with a history of ruptured membranes since Nov. 20, 1956. Significant past history included a right partial salpingectomy in 1952 for a tubal pregnancy. Her only child was born in 1954. Abdominal examination revealed a tender uterus, a small baby in a breech presentation, and absence of fetal heart tones. On sterile vaginal examination the cervix admitted one finger. The breech could be palpated. The patient was placed on antibiotics. Her temperature spiked to 100° F. on December 5, 6, and 7, and to 101.6° F. on December 8. Attempts at inducing labor on December 9 and 10 were unsuccessful and the patient was prepared for cesarean section.

When the peritoneal cavity was opened it was found that the uterus was enlarged to a size consistent with a 4½ months' gestation. A sac measuring 8 cm. in its greatest diameter was attached to the upper portion of the uterus. Both Fallopian tubes were identified and the right partial tube was found to enter the sac. The sac was inadvertently ruptured and a stillborn infant and placenta were delivered. Bleeding was profuse. A subtotal hysterectomy was performed. The postoperative course was uneventful and the patient was discharged on the eighth postoperative day.

Comment

Uteroabdominal pregnancy is an unusual and rare type of ectopic pregnancy. The first type is caused by a fistulous tract created by an instrument used in an attempted criminal abortion.

The suspicion of criminal interference in the second and third cases was aroused by the large fistulous communication and the old inflammatory changes visualized by the pathologist.

The case of uteroabdominal pregnancy following cesarean section was caused by disruption of a previous scar which permitted communication with the peritoneal cavity and the endometrium. The last case was one of angular implantation which could be explained on intrauterine trans-

cavity migration or passage through the remnant of the right tube.

The diagnosis must be differentiated from tubal pregnancy, fetal death in utero, threatened abortion, ovarian cyst, abdominal pregnancy, and pregnancy in a congenital anomalous uterus.

Summary

1. Uteroabdominal pregnancy is defined as a form of ectopic pregnancy where a portion of the fetus is outside of the uterus and a portion in the uterine cavity—or as a fistulous communication between the fetal membranes and endometrial cavity which would permit the passage of amniotic fluid or fetal appendages.

2. Uteroabdominal pregnancy may be caused by (a) attempted criminal abortion; (b) defective scar, either from cesarean section or salpingectomy; (c) angular implantation of ovum; (d) implantation of ovum in a stump of a tube.

3. Five illustrative cases are presented.

What is the actual present-day management of the placenta in late abdominal pregnancy?

Analysis of 101 cases

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Two patients with advanced abdominal pregnancy were admitted to the Cumberland Hospital within a period of 6 weeks. The occurrence of 2 such cases in an institution averaging approximately 2,000 deliveries per year prompted us to investigate the present-day management of the placenta in late abdominal pregnancy. Furthermore, the divergence of the situations encountered and the variation of therapy in the 2 cases led us to review and analyze 101 cases from the literature on this controversial and relatively rare situation. Concepts of the management of the placenta in abdominal pregnancy are not unanimous. Seventy-one years ago, Harris[43] discussed the problems associated with abdominal pregnancy and the wisdom of removal of the placenta. His basic reasoning and tenets were so simple and fundamental that they have remained relatively unchanged to the present time. However, the relative value of removing the placenta or leaving it in situ remains undecided.

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Presented at a meeting of the Brooklyn Gynecological Society, Nov. 19, 1958.

**Present address: Roswell Park Hospital, Buffalo, New York.*

Material

In an attempt to clarify this problem, we have collected and analyzed 101 cases which occurred in the third trimester of pregnancy and in which the management of the placenta was clearly described. Ninety-eight of these cases (including 2 repeat abdominal pregnancies) were collected from original case reports published in the world literature from 1950 to 1957. Another case from the Obstetrical Service of Dr. Louis Hellman at the State University of New York Downstate Medical Center, is included, the data having been forward by personal communication. To these are added 2 new cases from our Service. Cases that occurred before 1945 were excluded from the analysis.

Original case reports

Case 1. On July 27, 1955, L. W., a 30-year-old Negro woman, para 0-0-0-0, was admitted to the Surgical Service with intermittent pain and diarrhea of 2 weeks' duration; she was discharged to the Prenatal Clinic. The last menstrual period was May 1, 1955.

On Jan. 1, 1956, the patient was admitted with a diagnosis of early labor and syncope shortly prior to admission. Her temperature was 96.6° F., pulse 120 per minute, blood pressure 120/70, hemoglobin level 7 Gm. per cent, and she was apprehensive. While fetal heart sounds were present, no fetal parts and no distinct uterus

were felt. There was no bleeding and the cervix was soft, posterior, closed, and moderately tender on motion. Laparotomy was performed.

When the abdominal cavity was opened, approximately 1,500 to 2,000 c.c. of fluid and clotted blood were evacuated. An intact fetal sac occupied the entire abdominal cavity. A living grossly normal 3 pound, 15 ounce baby girl was delivered, the fluid being clear. The cord was clamped, divided, and ligated at the placental insertion. The uterus was enlarged to approximately 8 weeks' gestational size. The placenta was implanted on the anterior and left upper surface of the uterus, bladder, left broad ligament, pelvic wall, sigmoid colon, and the terminal ileum. There was slight bleeding present from the right superior edge of the placenta. The free edges of membranes were then trimmed off and the abdomen was closed. The blood loss was replaced.

One half hour later, the patient went into shock. Four hours postoperatively the abdomen was re-explored and approximately 2,000 c.c. of blood was encountered in the abdominal cavity. The placenta had partially separated. However, an attempt to separate it from the uterus was followed by a severe hemorrhage requiring subtotal hysterectomy. The abdomen was closed without drainage. The patient received a total of 5,000 c.c. of whole blood and other supportive therapy. At the end of the procedure, her condition was still critical.

*Pathology report** (Fig. 1). A placenta, 19 cm. in greatest diameter, was intimately adherent to the anterior and lower anterior fundal wall. The placenta was partially separated from the lower fundal wall by an irregular rent measuring 5 cm. in length. The cord was ligated short and eccentrically placed. A small dimpled elevation measuring 0.7 cm. in greatest dimension was seen on the anterior wall near the left horn of the uterine cavity.

Microscopy report (Figs. 2 and 3). Section through the sinus tract identified as a hemorrhagic dimpling on the left cornu showed definite decidua lining portions of the sinus tract with scattered fetal cells contained in the decidua and adjacent hyalinized myometrium. There were also fibrosed atrophied placental villi in other sections along the lining of the sinus tract tracing the course of the placental implantation from the cornu of the uterus to the extrauterine tissue. Sections of the endometrium show a well-formed decidua containing elongated endometrial glands lined by attenuated epithelium.

Diagnosis. Diagnosis was (1) ruptured cornual pregnancy; (2) secondary abdominal pregnancy, (3) gravid subtotal uterus, and (4) placenta (late gestation).

Postoperatively the patient was febrile for the first 4 days. She suffered an acute gastric dilatation and atelectasis of the right lower lobe which resolved on the fifth postoperative day. Recovery thereafter except for transient atelectasis was uneventful. She was discharged from the hospital on the twentieth postoperative day. During 9 months of follow-up she has remained asymptomatic.

The baby died on the nineteenth postpartum day. Autopsy revealed, in addition to bilateral bronchopneumonia, 6 lobes in the right lung and 4 lobes in the left lung. Other organs were normal.

Case 2. On Oct. 9, 1955, M. S., a 26-year-old Negro woman, para 1-0-0-1, was admitted to the Gynecological Service complaining of lower abdominal pain and vaginal bleeding of 3 weeks' duration. The last menstrual period was June 22, 1955. Examination revealed marked lower abdominal tenderness. The uterus was enlarged to the size of a 4½ months' gestation. The cervix was closed and there was a suggestion of a left adnexal mass. She improved and was discharged to the prenatal clinic with a diagnosis of intrauterine pregnancy. She returned for only one visit. On Feb. 11, 1956, 4 months later, she was admitted to the Obstetrical Service complaining of severe progressive abdominal pain and distension without external bleeding for 3 hours prior to admission. She was clammy and cold. The blood pressure was 108/70, pulse 120-140, respiration 32 per minute, hemoglobin level 7 Gm. per cent, hematocrit determination 21 per cent, and white blood count normal. The abdomen was markedly distended, tense, and tender. It measured 35 cm. from the symphysis to the fundus. The uterus and fetal parts could not be felt. There was an ill-defined pelvic mass of approximately 8 to 10 weeks' gestational size. A diagnosis of intraperitoneal hemorrhage and probable abdominal pregnancy at term was made. When the abdomen was opened, an anteriorly implanted placenta was inadvertently incised adding to the already blood-filled abdomen. An intact membranous sac occupied the entire cavity. The site of placental implantation ex-

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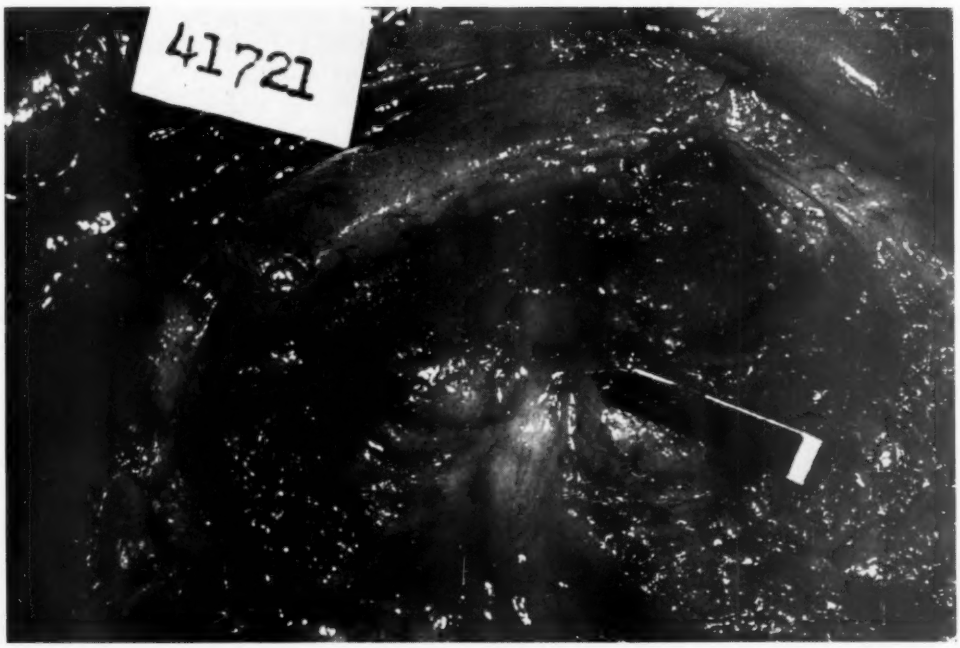


Fig. 1. Gross photograph of uterus magnified. Arrow points to sinus tract leading from endometrium through myometrium to site of perforation.

tended over the anterior abdominal wall from the pelvis up to 5 cm. below the umbilicus and to the left lateral pelvis and the bladder. The amniotic fluid was bloody. A living, 5 pound, 4 ounce grossly normal female infant was delivered and the cord was divided near the placental insertion. There was continuous bleeding from the pelvis. The bleeding appeared to come from the placental separation over the bladder. The placenta was removed manually, visible bleeding points were ligated, and the placental site was packed with 10 yards of 5 inch packing, which was brought out through the abdominal incision and the incision closed in layers; 3,000 c.c. of blood was given. The postoperative course was essentially uneventful. The patient was discharged from the hospital on the twelfth postoperative day. The infant developed icterus due to ABO incompatibility and died on the eighth postpartum day. Autopsy revealed intracranial hemorrhage.

Two weeks later a mass extended to 2 cm. above the umbilicus causing considerable discomfort and pain. The patient came to the hospital with a purulent discharge of 4 days' duration from an incisional sinus. Exploration revealed residual infected placental tissue in the region of the left adnexa, which was removed en block with the tube and ovary. The sinus was traced up to a subhepatic abscess, which was drained. The abdomen was drained and closed in layers. The postoperative course was satisfactory. The patient was discharged in good condition on June 18.

*Pathology report.** The specimen at the first operation revealed placenta with infarction (late gestation). Pathologic examination of tissue removed at the exploratory operation revealed hyalinized and calcified placenta and a paratubal organized hematoma and granuloma.

Analysis of 101 cases

I. Considerations prior to intervention.

1. Diagnosis. A correct diagnosis was made or considered in only 43 per cent before delivery. In the majority of these, the diagnosis was made too late for any intelligent planning. Urgent intervention was

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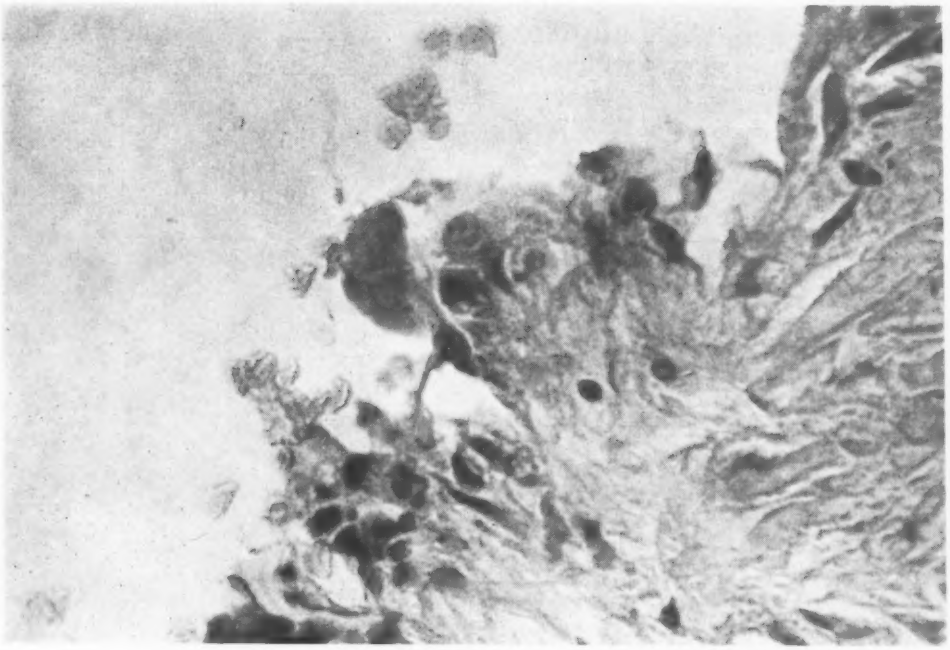


Fig. 2. Photomicrograph of lining of sinus tract shown in Fig. 1. Note fetal cells lining the sinus tract. (Original magnification ×350.)

usually indicated when the diagnosis was made.

2. *Viability of fetus.* In 54 per cent of the cases the fetus was living (Table I). To show the relationship of maternal complications to the length of time a dead fetus remained in situ, these cases were classified in three groups: (a) a fetus dead for less than 4 weeks; (b) fetus dead for more than 4 weeks; (c) time of fetal death undetermined.



Fig. 3. Photomicrograph of myometrium adjacent to sinus tract illustrated in Fig. 1. Arrow *A* points to fetal cells. Arrow *B* points to decidual cells within the myometrium. (Original magnification ×350.)

Table I. Complications prior to surgical intervention

	No.	Bleeding: Intraperitoneal bleeding: Less than 500 c.c.	Bleeding: Intraperitoneal bleeding: More than 500 c.c.	Bleeding: Intraperitoneal bleeding: Total	Bleeding: Into amnion	Bleeding: Into a viscus: Gastrointestinal	Bleeding: Into a viscus: Bladder	Total: No.	Total: %	Purulent infection of products of conception and/or peritonitis: No.	Purulent infection of products of conception and/or peritonitis: %	Toxemia of pregnancy: No.	Toxemia of pregnancy: %
Living fetus	55	3	5*	8	2	1	0	10	18.2	0	0	6	10.9
Dead fetus													
Less than 4 weeks	13	2	1*	3	1*	0	0	3		0		1	
More than 4 weeks	18	1	0	1	0	0	0	1		3		1	
Undetermined	15	0	0	0	1	0	1	2		1		2	
Total	46	3	1*	4*	2*	0	1	6	13.0	4	8.7	4	8.7
Total	101	6	6	12	4	1	1	16	15.8	4	4.0	10	9.9

*Same cases.

Table II. Management of placenta

		Removal of placenta: Complete: Without drainage	Complete: With drainage	Complete: Total	Complete: %	Partial: Without drainage	Partial: With drainage	Partial: Total	Partial: %	Total: No.	Total: %	Placenta left in situ: Without drainage	Placenta left in situ: With drainage	Placenta left in situ: Total	Placenta left in situ: %
	No.														
Living fetus	55	25	6	31	56.4	3	2*	5	9.1	36	65.5	14	5	19	34.5
Dead fetus															
Less than 4 weeks	13	5	3	8	61.5	-	-	-	-	8	61.5	2	3	5	38.5
More than 4 weeks	18	13	4	17	94.4	-	-	-	-	17	94.4	1	-	1	5.6
Undetermined	15	8	1	9	60.0	1	1	2	13.3	11	73.3	4	-	4	26.7
Total	46	26	8	34	74.0	1	1	2	4.3	36	78.3	7	3	10	21.7
Total	101	51	14	65	64.4	4	3	7	6.9	72	71.3	21	8	29	28.7

*In one case the placenta was partially removed and the remaining part was marsupialized.

Table III. Location of placenta*

	Placenta removed	Placenta partially removed	Placenta left in situ	Total	%
Confined to lower abdomen					
Intraligamentous	5	0	4	9	11.0
Confined to adnexa, broad ligaments, and uterus	10	2	2	14	17.1
Connected to upper genital tract	28	2	13	43	52.4
Not connected to upper genital tract	4	2	0	6	7.3
Total	47	6	19	72	87.8
Extending into or confined to upper abdomen					
Connected to upper genital tract	2	0	0	2	2.4
Not connected to upper genital tract	2	0	6	8	9.8
Total	4	0	6	10	12.2

*Number of cases evaluated, 82.

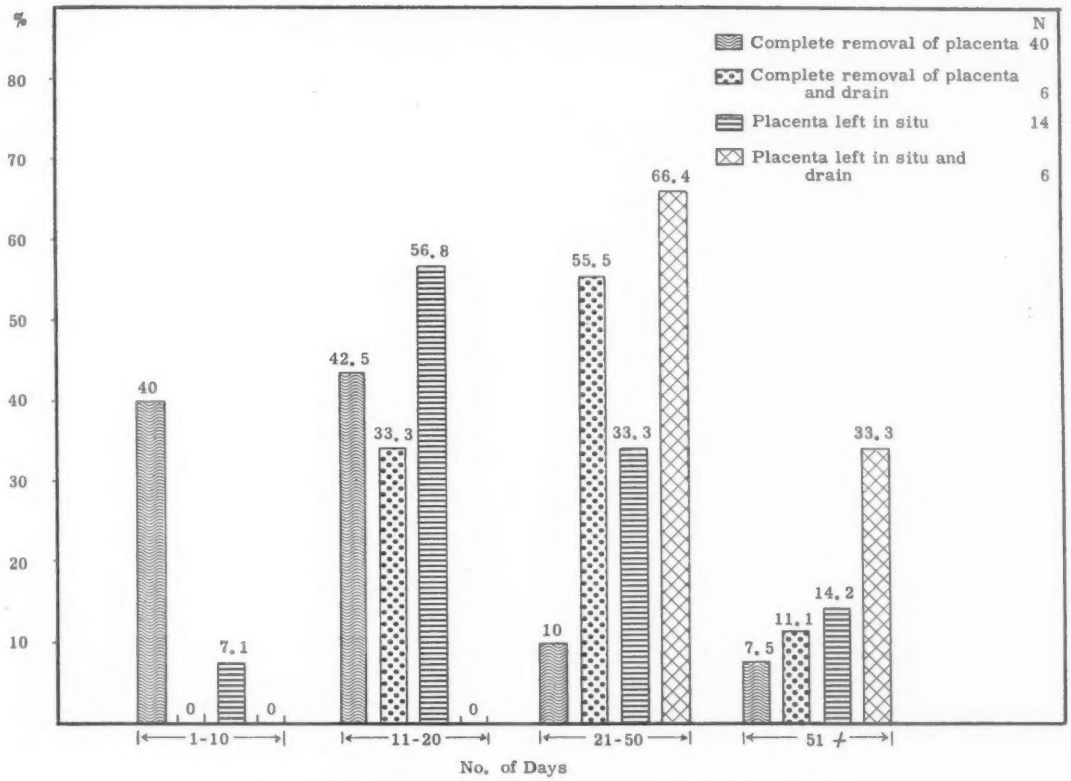


Fig. 4. Days of hospitalization (readmissions not included).

3. Complications.

A. BLEEDING. Bleeding occurred in 15.8 per cent. It occurred more frequently with a living than with a dead fetus. In 6 cases the bleeding was in excess of 500 c.c. and in 2 of these it was estimated at more than 1,000 c.c. The bleeding occurred intraperitoneally (retroperitoneally in cases of intraligamentous pregnancies), or into a viscus or amniotic sac.

B. INFECTION. Severe infection, as evidenced by generalized peritonitis or purulent infection of the gestational sac, was the second most formidable complication. It occurred only in those cases where a dead fetus was carried for more than 4 weeks. Such cases constituted 8.7 per cent of the cases with dead fetuses. Mild infections, as evidenced by a febrile course, occurred in all cases, frequently with no response to antibiotics and without findings of gross infection. It occurred most often in the group with a dead fetus. In 5 the fever itself was troublesome enough to precipitate the decision to intervene surgically.

C. TOXEMIA. Toxemia of pregnancy occurred in 9.9 per cent, supporting the view of Portuondo Valdor[105] that it is more frequent with abdominal than with uterine pregnancy. One case of pre-eclampsia[30] led to postpartum eclampsia.

D. MISCELLANEOUS COMPLICATIONS. There were other less frequent complications—2 intestinal obstructions and one fistula between the amniotic sac and the bowel. In one case, sensitization of the mother to a dead fetus occurred as evidenced by a generalized skin rash. General malaise, anemia, gastrointestinal disturbances, and abdominal pains were rather common, irrespective of whether the fetus was alive or dead. Complaints of this type necessitated repeated admission to the hospital and often precipi-

Table IV. Detailed attachments of placenta*

	Placenta removed	*Placenta partially removed*	*Placenta left in situ*	*Total*	*%*
Uterus	28	3	5	36	49.3
Adnexae	35	3	11	49	67.1
Cul-de-sac	4	1	3	8	11.0
Posterolateral pelvic wall	4	1	3	8	11.0
Iliac fossa	8	2	2	12	16.4
Bladder	4	1	1	6	8.2
Anterior abdominal wall	5	1	4	10	13.7
Posterior abdominal wall	0	0	2	2	2.7
Rectosigmoid, cecum, ascending and descending colon	16	2	8	26	35.6
Appendix	2	0	0	2	2.7
Transverse colon	3	0	2	5	6.8
Small intestines	7	0	4	11	15.0
Mesentery	3	0	3	6	8.2
Stomach	1	0	1	2	2.7
Spleen	1	0	0	1	1.4
Diaphragm	1	0	0	1	1.4
"Region of spleen and left kidney"	0	0	1	1	1.4

*Number of cases evaluated, 73.

tated the decision to intervene surgically. Of interest is a case of a dead fetus which remained in situ for 25 years before symptoms led to laparotomy.[14]

II. Surgical intervention.

1. Surgical approach. In only 3 cases,[38, 58] probably all intraligamentous, was delivery effected vaginally. In all others the abdominal approach was used.

2. Management of placenta. Table II shows that the placenta was removed in 71.3 per cent—completely in 64.4 per cent and partially in 6.9 per cent. It was left in situ in 28.7 per cent. The following techniques were used in its management:

A. Removal of all products of conception *in toto* with or without preceding aspiration of amniotic fluid. This was done in some

Table V. Management of bleeding*

	Preoperative bleeding†						*Bleeding due to incision of placenta when entering abdomen*
		Dead fetus					
	Living fetus	*Less than 4 weeks*	*More than 4 weeks*	*Undetermined*	*Total*	*Total*	
Partial removal of placenta	1(B)	–	–	–	–	1	1(B)
Partial removal of placenta and hysterectomy	1(C)	–	–	–	–	1	–
Complete removal of placenta	1	–	1	–	1	2	–
Complete removal of placenta and hysterectomy	–	–	–	–	–	–	–
Complete removal of placenta and cesarean hysterectomy	–	–	–	–	–	–	–
Complete removal of placenta and resection of bowel	–	1	–	–	1	1	–
Complete removal of placenta and splenectomy	–	–	–	–	–	–	–
Total cases treated by removal of placenta	3	1	1	–	2	5	–
Placenta left in situ, other methods employed‡	4	1(A)	–	–	1	5	–
Total number of cases	7	2	1	–	3	10	–

*Number of cases evaluated, 101. (A) (B) (C) (D) = same cases.

†Only cases with active bleeding still present at the time of laparotomy are included.

with a previously dead fetus and infected or presumably infected gestational sac.

B. The fetus was delivered first, followed by the entire placenta. Most times adherent membranes were left behind and the blood vessels supplying the placenta were not ligated prior to removal. In one case excision was from a bloodless field.[82]

C. Partial removal was done in 7 in the presence of bleeding where complete removal was not possible.

D. It was left in situ in 29. In all the cases but one, the remaining sac was left open. The abdomen was drained more frequently than might have been indicated by the presence of hemorrhage or infection.

3. Factors determining the management of the placenta. We divided these factors into two groups: (A) factors inherent in the nature of the placenta itself, viz., location, blood supply, shape and state of vitality; (B) complications present at the time of operation.

A. Eighty-two adequately described cases were evaluated for location of the placenta (Table III). Eleven per cent of these were intraligamentous. The placenta was confined to the lower abdomen in 87.8 per cent. In 12.2 per cent, it extended to or was confined solely to the upper abdomen. The adnexa, broad ligaments, and uterus were the principal sites of implantation in 82 per cent. From there, the placenta extended in either direction to the pelvis, abdominal wall, and abdominal viscera. In 17.1 per cent, it was confined wholly to the adnexa, broad ligaments, and uterus. Consequently, in the majority, the placenta received its principal blood supply from the ovarian and uterine vessels. Only 17 per cent received their blood supply from sources other than the genital tract. This last figure is in all probability still lower since exploration was not always sufficiently extensive to determine the blood supply in those cases where the placenta was left in situ. Table IV shows the detailed attachments of the placentas. The most common type of placental shape was discoid. The less common and easiest to remove was the pedunculated type. The least frequent and least adaptable for removal was the widespread, irregular, and multilobed placenta. With a fetus dead for more than 4 weeks, the placenta was removed more frequently than in other cases (Table II). The danger of hemorrhage from placental removal persisted when the fetus was dead. This occurred twice with a fetus dead for more than 4 weeks (Table V), one presenting a dead fetus of 7 years wherein the

Bleeding due to exploration							*Severe bleeding due to attempt to remove placenta*						
	Dead fetus							*Dead fetus*					
Living fetus	*Less than 4 weeks*	*More than 4 weeks*	*Undetermined*	*Total*	*Total*	*Total*	*Living fetus*	*Less than 4 weeks*	*More than 4 weeks*	*Undetermined*	*Total*	*Total*	*Grand total*
1	–	–	–	–	1	2	–	–	–	–	–	–	2
1[C]	–	–	–	–	1	1	–	–	–	–	–	–	1
1	–	1	–	1	3	6	3	1	–	1	2	5	11
1	–	1	–	1	2	2	2	1	–	–	1	3	5
						1							
1[D]	–	–	–	–	1	1	1[D]	–	–	–	–	1	1
	1	–	–	1	1	2	–	–	–	–	–	–	2
	–	–	–	–	–	–	1	–	–	–	–	1	1
1	1	2	–	3	9	14	7	2	–	1	3	10	23
1	–	–	–	–	2	8	1	1[A]	–	2	3	4	11
4	1	2	–	3	11	22	8	3	–	3	6	14	34

†Suture ligature of bleeding area, ligature of uterine or ovarian vessels, packing, etc.

placenta was still well preserved,[85] and the other a fetus that had been dead for several years.[40]

B. Complications at the time of operation were another factor frequently determining the management of placenta. The most important complication was bleeding. Its management is shown in Table V. The bleeding, however, was an indication for removal of the placenta in only 19 per cent. Twenty per cent of the total number of hysterectomies were done for bleeding due to attempts at separation of the placenta. All 4 cases complicated by purulent infection were treated successfully by removal of the products of conception. Toxemia of pregnancy may have been a contributing factor in deciding to remove the placenta in at least one case of a dead fetus.[80] The case complicated by a fistula between the amniotic sac and the bowel was treated by removal of the placenta and closure of the fistulous opening in the bowel and temporary colostomy.[83] The management of abdominal pregnancy secondary to or associated with spontaneous rupture of the uterus, dehiscence, or rupture of the uterine scar from previous cesarean section or myomectomy is illustrated in Table VI. Table VII shows the management of 4 cases of multiple abdominal pregnancy.

4. Concomitant operation. Additional surgical procedures were necessary in 76.4 per cent of cases where the placenta was removed. Table VIII indicates the type of operation that was performed. Noteworthy is the observation that hysterectomy was done in 27.8 per cent of these cases.

III. Mortality and morbidity. Mortality in this series was 2 per cent (Table IX). One of these patients was delivered vaginally[58] and another by laparotomy with the placenta left in situ.[31] Comparison of these results with previously reported mortality for abdominal pregnancy indicates a marked drop in its rate (Table IX). Previous reports show that the rate was higher when the placenta was left in situ and lower when removed (Table X).

Morbidity was most difficult to evaluate clearly because different criteria were used for defining morbidity and presentation of cases was not always complete. Follow-up was often inadequate. This distorts attempts

Table VI. Management of cases with defect of the uterine wall

Etiology	*No. cases*	*Findings at operation*	*Operation*	*Remarks*
Spontaneous rupture of uterus	1	Healed scar on posterior surface of uterus	Removal of placenta and subtotal hysterectomy	
Rupture (or dehiscence) of uterine scar from previous cesarean section	3	A. Not stated	Placenta left in situ	One year after operation hysterography revealed sinus in the uterine wall suggestive of previous rupture of operative scar
		B. Rupture of uterine wall	Closure of defect after débridement of wound edges and placenta left in situ	Placenta was located in right upper quadrant
		C. Rupture of uterine wall	Removal of placenta and subtotal hysterectomy	
Rupture of uterine scar post myomectomy	1	Absence of posterior uterine wall	Removal of placenta and hysterectomy	

Table VII. Multiple abdominal pregnancy (4%)

No.	*Type of pregnancy*	*Type of delivery*	*Mother*	*Babies*	
				a	b
1	Intra-abdominal (a + b)	a, b } Laparotomy	Living	Living	Living
2	Heterotopic a. Intrauterine b. Intra-abdominal	a. Spontaneous vaginal delivery b. Laparotomy 3 days later	Living	Living	Living
3	Heterotopic a. Intrauterine b. Intra-abdominal	a. Spontaneous vaginal delivery b. Laparotomy 61 days later	Living	Living	Living
4	Heterotopic a. Intrauterine b. Intra-abdominal	a, b } Laparotomy plus cesarean hysterectomy	Living	Living	Living

at evaluation, particularly where the placenta was partially removed or left in situ. One should view the data in Tables XI and XII with this in mind.

Fig. 4 indicates that the postoperative hospital stay of patients with the placenta left in situ was longer than that of patients with the placenta removed. The relatively high incidence of readmissions in the former accentuates this fact even more.

The postoperative morbidity (Table XI) was considerably higher when the placenta was left in situ. The most serious complications associated with leaving the placenta in situ were secondary bleeding from placental separation, formation of intra-abdominal abscesses requiring drainage, and intestinal obstruction. A distressing complication in this instance was the spontaneous extrusion of placental fragments over a period of several months and persistent abdominal sinuses. Finally, a large majority of the patients with the placenta left in situ suffered abdominal pain, intermittent fever, toxicity, or general malaise over a period of months and even years, whereas those with the placenta removed did not.

The necessity for readmission where the placenta was left in situ was probably higher than 25 per cent (Table XI), but follow-ups are inadequately reported. This is also true for the incidence of secondary laparotomies

Table VIII. Concomitant operation in 72 cases where placenta was removed

Type of operation	*No.*	*%*
Hysterectomy (with or without removal of adnexa)	20	27.8
Removal of adnexa, unilateral or bilateral, no hysterectomy	21	29.2
Appendectomy	5	6.9
Resection of bowel	1	1.4
Resection of bowel (and temporary colostomy)	1	1.4
Closure of bowel defect (and temporary colostomy)	1	1.4
Repair of bowel serosa	2	2.8
Splenectomy	1	1.4
Repair of uterine rupture	1	1.4
Hysteropexy	1	1.4
Suprapubic drainage of bladder	1	1.4
Total cases with operation	55	76.4
No concomitant operation	17	23.6

Table IX. Maternal mortality

Name of author	*No. cases*	*For years*	*Mortality*	
			No.	*%*
Harris	27	1816-1886	24	88.9
Hellman and Simon	316	1809-1933	101*	31.9
Ware	249	1933-1948	37	14.9
de Villiers	77	1944-1954	4†	5.2
Hreshchyshyn, Bogen, and Loughran	101	1945-1957‡	2	2.0

*Results of 3 cases unknown.
†One case post mortem.
‡Cases published 1951 and after.

Table X. Relation of mortality to management of placenta

Author	Year published	No. cases	Placenta removed			Placenta partially removed			Placenta left in situ		
			No. cases	Died	%	No. cases	Died	%	No. cases	Died	%
Beck	1919	201	137	23	16.7	–	–	–	64	26	40.6
de Villiers*	1954	77	39	1	2.6	2	0	0	34	2	5.9
Hreshchyshyn, Bogen, and Loughran		101	65	0	0	7	0	0	29	2†	6.9

*One case diagnosed post mortem not included. No operation in one case—fetal remains discharged per rectum.
†One patient died after vaginal delivery.

(Table XII). The necessity of secondary removal of the placenta because of secondary hemorrhage, persistent pain, intermittent partial intestinal obstruction, and drainage of abscesses were the most frequent indications for secondary laparotomy. In 2 cases, one 79 days[88] and another 2 months[93] post partum, the removal of the placenta was associated with considerable bleeding.

Comment

A timely diagnosis of abdominal pregnancy is essential to an intelligent plan of treatment. The question of elective operation arises in those cases diagnosed early with no complicating factors to indicate the necessity of immediate operation. Two different situations present themselves for consideration depending on whether the fetus is alive or dead. A waiting policy has been advised by Jarcho[53] and others[23, 63, 80] with a live baby near viability, in order to increase the survival rate of the infant. Contrariwise, many authorities[29, 47, 67, 69] feel that because of the low survival rate of infants, the high incidence of anomalies in the fetus, and particularly because of the potential hazards of maternal complications, immediate surgical intervention is preferable. De Magathães Netto[74] observed that operation is rendered more difficult with a longer wait because the placenta involves larger areas.

Where the fetus is dead, opinions are again divided as to the ideal time to terminate the pregnancy. One view held is that postponing the operation 4 to 6 weeks after fetal death results in regression of the placenta to a point where it can be removed without too much risk to the mother.[41, 67] To promote this effect, the use of testosterone[80] and x-ray[62] have been advised. Others[29, 46, 47] are of the opinion that potential hazards of infection, perforation of the bowel, and separation of the placenta with resultant hemorrhage are too great to justify a waiting policy. Therefore, they favor immediate intervention.

Of interest are the speculations on the causes of complications. Granjon[41] feels that it is the lack of decidual formation which

Table XI. Postoperative course

	No. cases	Complications				
		Intra-abdominal abscess (requiring drainage)	Extrusion of placenta through abdominal wound	Evisceration	Intestinal obstruction	Intra-abdominal bleeding
Complete removal of placenta	65	–	–	1	–	–
Partial removal of placenta	7	1	–	–	–	–
Placenta left in situ	29	3	4	1	3	3
Total	101	4	4	2	3	3

*Such as abdominal wound infection, abdominal pain, intermittent fever, toxicity, anemia, and general malaise.

predisposes to separation of the placenta effecting intraperitoneal bleeding. We noted a rather frequent velamentous insertion of the cord and consider this as a possible explanation for bleeding into the amniotic sac. Portuondo Valdor and Barata Rivero[105] described bleeding into a viscus due to erosion of a blood vessel by the trophoblast. The proximity of the gestational sac, particularly the chorionic villi, to the gastrointestinal tract is offered as an explanation for infection by several authors.[29, 67, 105] Another cause of infection may be perforation of the uterus due to instrumentation with a sound to measure the uterine cavity or to rupture the membranes in what is erroneously presumed to be an intrauterine pregnancy. Perforation occurred in 2 cases in this series.[78, 103] We also noted an increased incidence of infections among the cases where, prior to establishing the diagnosis, a medical induction of labor was attempted.

Surgical intervention was not an accepted procedure in ancient times. It was left to the mother to dispose of the fetus.[107] Primarose in 1595[9, 56] was the first to describe a case treated with laparotomy. The first case managed by vaginal delivery was reported in 1817 by King[38, 53] in this country. Incidentally, there are those who still claim good results with this procedure.[1] In this country, because of the great risk to the mother, it has been abandoned completely in favor of the abdominal approach.

During the early attempts at operative management, it became obvious that removal of the placenta may be associated with severe hemorrhage. For this reason Turnbul of London in 1791 and Mease of Philadelphia in 1795[43] advised leaving the placenta in situ. Beck of Brooklyn[10] lent support to this idea, based on his own studies with placental transplants in dogs. He advised that the placenta be left in situ when the blood supply could not be easily ligated. Leaving the placenta is not without its disadvantages because of associated morbidity. Marsupialization, introduced in 1855 by Lazarewicz[43] of Charkiv (Ukraine), fell gradually into disfavor.

Currently, there are authors who take the extreme view in giving almost exclusive preference either to leaving the placenta in situ[101] or to removing it.[105] Our review shows that both procedures are presently widely practiced; removal of the placenta being done more frequently than leaving it in situ. We feel that both procedures are justified. In deciding which of them to employ in a particular case, it is important to appreciate certain pertinent facts. In recent years there has been a marked decrease in the mortality of patients with abdominal pregnancy regardless of the procedure elected. This is undoubtedly a reflection of the general advances in surgery, particularly the availability of large amounts of blood and antibiotics. The data obtained in this series are not sufficiently extensive to demonstrate a significant difference in mortality between the two procedures. However, the morbidity in cases where the placenta was left in situ is much higher and this fact makes removal

			Readmissions				
			No. of readmissions				
*Miscellaneous**	*Total*	*%*	*1*	*2*	*3*	*Total*	*%*
11	12	18.5	–	–	–	–	0
2	3	42.9	1	–	–	1	14.3
7	21	72.4	5	1	1	7	24.1
20	36	35.6	6	1	1	8	7.9

Table XII. Secondary operations

		No. laparotomies					
		1	*2*	*3*	*Total*	*%*	*Type of operation performed*
Complete removal of placenta	65	6	-	-	6	9.2	2 closures of colostomy; 1 closure of evisceration; 1 removal of peritoneal cyst; 1 removal of Miller-Abbott tube that was accidentally cut off and lost in gastrointestinal tract; 1 exploratory laparotomy for intestinal obstruction (no obstruction found)—decompression of jejunum.
Partial removal of placenta	7	1	-	-	1	14.3	1 removal of residual placenta and drainage of subphrenic abscess.
Placenta left in situ	29	7	2	2	11	37.9	7 removals of placenta; 2 marsupializations of placenta; 3 drainages of intra-abdominal abscesses, 1 closure of evisceration; 1 exploratory laparotomy for shock (patient died during the operation from hemorrhage); 1 nephrostomy; 1 removal of intestinal obstruction; 1 excision of fistula and salpingectomy.
Total	101	14	2	2	18	17.8	

of the placenta desirable. Our analysis supports the view of Holland and Bourne[47] that removal of the placenta is free of risk in most cases. In addition to avoiding bleeding by carefully opening the abdomen and not disturbing the placenta at exploration, the surgeon could also diminish the hazards of bleeding by correct appreciation of topographic conditions present. Our evaluation indicates that in the great majority of cases the principal blood supply to the placenta comes from the ovarian and uterine arteries. In the remaining cases, it may be presumed that the placenta is supplied from the arteries of the organ which is the principal site of placental attachment. In electing to remove the placenta and also when confronted with bleeding from a partially separated placenta, it is of the utmost importance that one recognize and ligate all avenues of arterial blood supply. Occasionally it may be of advantage to remove the organ to which the placenta is attached. Elective removal is contraindicated if it is not certain that the tributary arteries can be ligated.

It is of interest to note that although placental attachment to intestines is rather common, as indicated by our findings and those of others,[80] removal of the placenta seldom resulted in bowel injury in the cases surveyed, and bowel resection was rare.

Complications which are present at the time of operation may be factors modifying the management of the placenta. Partial removal may be necessary when an incompletely detached portion is bleeding and complete removal is impossible.

Marsupialization has been recommended in the presence of infection.[9] Such a case, which was reported from our institution in 1943,[64] demonstrates that this procedure may be associated with a long-lasting postoperative morbidity. In the present series, all 4 cases complicated by purulent infection were treated successfully by removal of the products of conception. These products should be removed *in toto,* if possible. Stoeckel[6] advised one to proceed in the same way as in the case of a large ovarian cyst and to remove the placenta only after the entire membranous sac was mobilized.

The presence of a fistula between the amniotic sac and the bowel may require resection of the bowel. In the case included in the present series, the opening in the bowel was closed and a temporary colostomy was performed. The outcome for the patient was excellent. This is a serious complication, however, and can prove disastrous.[68]

Toxemia of pregnancy may call for removal of the placenta if one is to accept the view[80] that toxemia may persist as long as the trophoblast is living.

Multiple abdominal pregnancy becomes a dual problem. In cases of heterotopic pregnancy Nandi[72] feels that the normally located fetus should be delivered first vaginally, while Vasicka and Grable[107] are of the opinion that both fetuses should be delivered at the same time by the abdominal route. In multiple intra-abdominal pregnancy, we suggest that the same rules apply as for a single abdominal pregnancy.

Summary

1. One hundred and one cases of advanced abdominal pregnancy have been studied and analyzed. The management of this condition is considered.

2. The high rate of complications prior to intervention indicates that early intervention probably offers the patient a better prognosis, regardless of whether the fetus is alive or dead.

3. Currently, removal of the placenta is the more frequently practiced procedure.

4. The choice of procedure depends on the topographic conditions and complications present at the time of operation. Removal of the placenta is possible without endangering the life of the patient in the majority of cases. We believe that when it is surgically feasible the placenta should be removed.

5. The low mortality rate in this series, thought to reflect in large part the general advances in medicine, does not allow us to draw any conclusions in regard to the relationship of the type of management of the placenta and maternal death. Statistical data from previous years show that the mortality rate was higher when the placenta was left in situ and lower when it was removed.

6. The high morbidity rate associated with leaving the placenta in situ in this series of cases makes the removal of the placenta desirable.

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Abdominal pregnancy with vaginal leakage of amniotic fluid

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ABDOMINAL pregnancy, with an incidence of one in every 15,000 pregnancies, is an uncommon and serious condition. Ware,[1] in his analysis of 249 cases of extrauterine pregnancy of more than 7 months' duration collected from the literature from 1935 to 1946, reported a maternal mortality of 14.85 per cent. Suter and Wichser[2] found that only about one fourth of all the extrauterine pregnancies diagnosed after the fifth month of gestation result in living, viable babies. About one third of these babies will have major or minor deformities including those which are incompatible with life.

Thus, it is of interest to report an unusual case of abdominal pregnancy that had leakage of amniotic fluid vaginally through an amniotubal fistula for several months prior to termination of the pregnancy by laparotomy.

Case report

L. B., a 33-year-old Negro woman, gravida i, para 0, whose last menstrual period was June 17, 1954, was first seen on Oct. 12, 1954, because of the leakage of amniotic fluid since the middle of September, 1954. The estimated date of confinement was March 24, 1955. On Aug. 1, 1954, the patient had experienced a sudden pain in the right lower quadrant with fainting spells. This pain and fainting recurred twice and required sedation by a private physician. Past history revealed a left salpingo-oophorectomy and appendectomy for a left tuboovarian mass. No fibroid was noted at the time of this operation in November, 1951.

At the first prenatal visit, her blood pressure was 150/90, her weight was 143½ pounds, and her height was 5 feet, 4 inches. The urine was normal; the hemoglobin level was 10.4 Gm. per cent; the red blood count was 3.7 million; the white blood count was 8,200 with a normal differential. On pelvic examination the uterus seemed to be small and separate from a large, firm mass in the right adnexal region. The nitrazine test was positive. Tentative diagnoses were abdominal pregnancy (leaking fluid?) or pregnancy in an accessory horn of a bicornuate or fibroid uterus. The patient was placed on progesterone and bed rest.

On the second visit on Oct. 25, 1954, examination revealed pronounced leakage of amniotic fluid. The patient was placed on oral stilbestrol. An Aschheim-Zondek test was ordered on Nov. 8, 1954, and was found to be positive. On Dec. 16, 1954, the examiner definitely decided that the patient had an abdominal pregnancy with leakage of amniotic fluid through a fistulous tract from the amniotic sac through the tube to the uterus. The patient was advised of the risk and a decision was reached to try to carry her to near term in an effort to deliver a living, viable baby.

X-ray examination of the abdomen on Jan. 17, 1955, revealed a fetus deep in the posterior cul-de-sac. No uterine shadow was seen. The fetus seemed small and probably would not have lived if the pregnancy had been terminated at this point. There was no more leakage of fluid.

The patient took a trip to Arkansas without consulting her doctor. On her return on Jan. 30, 1955, no fetal heart tones were audible.

The patient was admitted to Provident Hospi-

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Presented before a meeting of the Chicago Gynecological Society, March 20, 1959.

tal on Feb. 3, 1955, because of vaginal bleeding. There was no associated pain at this time. The patient stated that she had had lower abdominal pain while in Arkansas. The urine was normal; the hemoglobin level was 9.8 Gm. per cent; the red blood count was 3.4 million.

A sterile vaginal examination revealed the uterus and cervix pulled high into the abdominal cavity and seemingly separate from the fetus. Introduction of a probe into the uterus showed the length of the cavity to be 13 cm. The fetal head was still felt in the posterior cul-de-sac. Five minims of Pitocin was administered subcutaneously, according to the technique of Cross and associates.[3] No contractions were felt over the fetal mass; however, the small uterus did contract. No round ligaments were palpable and Braxton Hicks contractions had never been noted. The diagnosis of abdominal pregnancy with fetal death was confirmed. A hysterogram had not been taken because of difficulty in exposing the cervix.

On Feb. 5, 1955, a laparotomy was performed under spinal anesthesia (Pontocaine, 12 mg.). The uterus was anterior, slightly enlarged, and displaced slightly to the left. A macerated, premature female fetus was free in the abdominal cavity with the fetal head wedged in the posterior cul-de-sac over the sacrum (Fig. 1). The placenta was implanted in the distal end of the right Fallopian tube, lateral pelvic wall, and large bowel posteriorly. There was marked ecchymosis of the sigmoid colon. The fetus was removed from the abdominal cavity. The placenta was inspected and left in situ. The fistulous tract in the right Fallopian tube was demonstrated and repaired. The blood loss was approximately 200 c.c. The patient received 500 c.c. of blood during the procedure and left the operating room in excellent condition. She was discharged on the eighth postoperative day.

The pathologist's report showed a macerated premature fetus without anomalies.

Subsequent course. The patient has been followed closely for the past 4 years and her course has been uneventful. At the present time the placenta has been almost completely absorbed. A lemon-sized mass is still palpable in the right adnexal region.

Comment

This patient had a previous salpingo-oophorectomy for adnexal disease. Her desire to have a baby was great. Thus, when the diagnosis of abdominal pregnancy was definitely established, in spite of the increased hazard to the mother and the decreased chance of securing a living, viable baby, a decision to carry the patient to 36 weeks' gestation was made. When fetal death occurred, however, the pregnancy was terminated by laparotomy. The persistent leakage of amniotic fluid clouded the picture early and taxed the diagnostic acumen of the examiner.

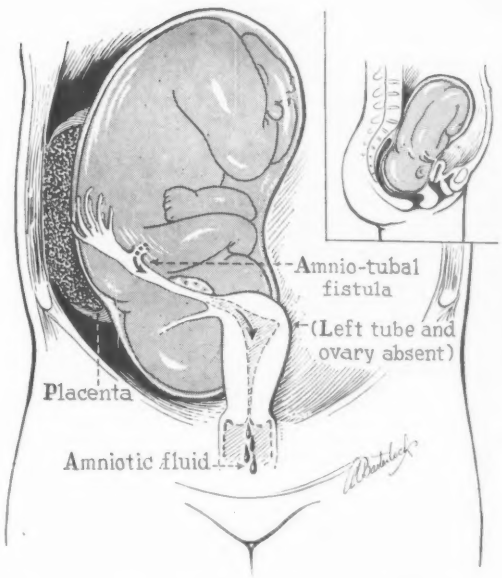


Fig. 1. Diagrammatic drawing showing fistula from amnion into Fallopian tube.

Summary

1. A case is presented of abdominal pregnancy with vaginal leakage of amniotic fluid through an amniotubal fistula.

2. The pregnancy resulted in an antenatal stillbirth.

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Unruptured primary ovarian pregnancy

A case report

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BECAUSE of its relative rarity, primary ovarian pregnancy is seldom kept in the forefront when differential diagnosis of an ovarian mass is considered. This case report is added to the literature simply to punctuate some of the pertinent factors aiding in the diagnosis.

The records of this hospital enumerate 11,156 uterine pregnancies during the last decade. Further, 316 ectopic pregnancies are listed, making a ratio of 1:348. The present case is the only recorded primary ovarian pregnancy. The literature discloses an incidence of primary ovarian pregnancy as ranging from one for every 25,000 to one for every 40,000 uterine pregnancies.[2-6] The rate of ectopic pregnancy varies from one for every 200 to one for every 300 uterine pregnancies.[2, 3, 5]

A 32-year-old white woman, gravida i, para i, consulted her doctor because of fatigue and "loss of pep" of about 2 months' duration. Her last menstrual period had taken place 2 months previously. The menses had been regular, occurring every twenty-eighth day and lasting for 5 days. The menarche was at 15 years of age. Eleven years prior to admission she was delivered of a mature male infant after an uneventful pregnancy.

Nine days before this hospitalization, that is, 7 weeks after the last menstrual period, the patient experienced a heavy bloody vaginal discharge with large blood clots. At first profuse, this bleeding subsided gradually after the ninth day.

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Physical examination on admission revealed a patient in good general health in no acute distress. The abdomen was soft and flat. There was considerable tenderness in the right lower quadrant. The vaginal examination disclosed a firm, closed cervix and a uterus of normal size. There was a tender cystic mass of about the size of a baseball in the right adnexal region.

The oral temperature was 98.6° F.; blood pressure 125/65; pulse rate 65; respirations 18. Laboratory data included: red blood count 4.25 million; hemoglobin level 10.2 Gm. per cent; white blood count 6,700. Urine findings were within normal limits. The presumptive diagnosis was right ovarian cyst. Uterine curettage was performed and yielded a small amount of tissue. Laparotomy was then performed.

The pelvic exploration revealed fibrous adhesions over the left ovary and the left tube was slightly distended and thickened. The right adnexa were adherent and the right ovary was cystic, purplish red, and firm. Right salpingo-oophorectomy was performed.

Pathology report. In the right adnexa there was a cystic doughy ovarian mass measuring 8.2 by 7.4 by 4.9 cm. The right Fallopian tube revealed the fimbrial end fused to the ovary, but a probe could be admitted into the entire lumen. On section the ovary was found to have a unilocular cyst filled with hemorrhagic fluid in blood clot. In one area there was a fetus which measures 1.4 cm. in crown-rump length. The wall of the cyst was spongy and purplish black. The surrounding tissue was spongy and villous. The ovarian cortex was distended and the serosa was discolored purplish black.

Microscopic description. Serial blocks of the ovary and Fallopian tube revealed an intact tubal wall and evidence of decidual reaction in the subepithelial region.

The wall of the ovary became distended by an amniotic sac having a thick decidua, chorionic villi with fibrous cores, atrophic trophoblast, and considerable blood clot (Figs. 1 and 2). There were venous channels in the mesovarium filled with red cells.

Sections of the proximal ovary and Fallopian tube disclosed an intact tubal wall and the ovarian stroma enclosed a hemorrhagic corpus luteum.

The fimbrial end of the Fallopian tube had some edematous mucosal folds with a sprinkling of lymphocytes and neutrophils. The subserosa had similar inflammatory cells.

Diagnosis. Primary, unruptured right ovarian pregnancy. A pregnancy test (rat) was positive on the day after operation.

Comment

The pathogenesis of ovarian gestation may be either fertilization of an ovum before extrusion from its Graafian follicle or fertilization of the ovum outside the ovary and its subsequent nidation upon the ovary. There are three types of ovarian pregnancy: (1) intrafollicular, the ovum being fertilized within its follicle; (2) superficial, the im-

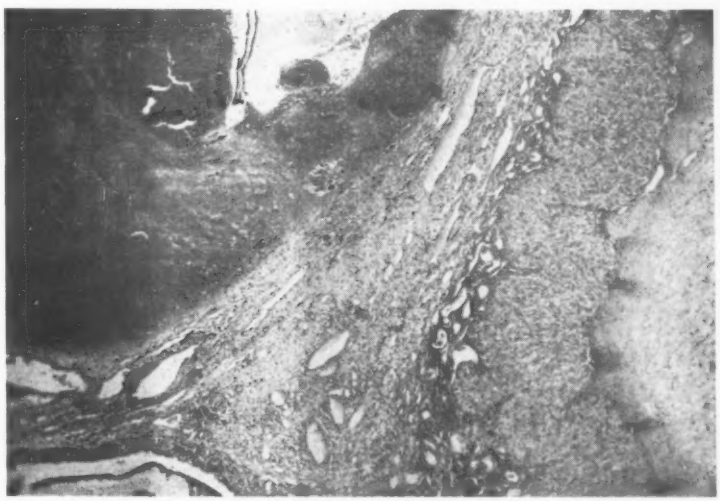


Fig. 1. Right ovarian stroma enclosing decidua of gestational sac with its blood clot and chorionic villi. Corpus luteum of pregnancy lies at right. (Hematoxylin and eosin. ×17.5.)



Fig. 2. Chorionic villi lying in blood clot adjacent to decidua. (Hematoxylin and eosin. ×50.)

plantation taking place on the ovarian surface; (3) interstitial, the nidation taking place in the ovarian stroma. The intrafollicular type is the most common.[4] Reports of ovarian pregnancy in ovaries with endometriosis have attempted to establish this as one of the etiological agents.[1] However, endometrium is not necessary for implantation of the fertilized ovum. This is demonstrated in complete placenta accreta where implantation occurs in myometrium devoid of endometrium.[3]

The difficulty of preoperative diagnosis of ovarian pregnancy has been previously emphasized. If the history is suggestive of ectopic gestation, tubal pregnancy has taken precedence because of greater statistical frequency.

However, a review of the literature suggests several clues which may strengthen the index of suspicion in favor of ovarian gestation. First, these patients have had a period of sterility of many years' duration. There may be a history of previous ectopic pregnancy. The age of these patients falls within the third and fourth decade.[4] On physical examination, breast changes are present infrequently. Abdominal tenderness is the most common complaint. An adnexal mass is palpable but most often cannot be differentiated from tubal pregnancy. Passage of a decidual cast followed by uterine bleeding aids in diagnosis of ectopic pregnancy. Endometrial curettage, determination of chorionic gonadotropic hormones, and a positive pregnancy test are important contributions to the diagnosis.

Depending on the proximity of the implanted pregnancy to the surface of the ovary, rupture with hematocele may occur at any time after the fifth week.[4]

The often quoted Spielberg criteria[5] are satisfied by the pathologic findings in the case reported; namely, the Fallopian tube was preserved and was separate from the ovary; the gestational sac was completely embedded within the ovary; the ovary and its chorionic sac were supported from the uterus by the uteroovarian ligament; ovarian tissue was incorporated in the wall of the chorionic sac.

Summary

Primary, unruptured ovarian pregnancy is reported in a 32-year-old gravida i, para i, with an 11 year history of infertility. The menses had always been regular, the last occuring 7 weeks prior to admission. There had been vaginal bleeding for 9 days. A tender right adnexal mass was palpable. Endometrial curettage resulted in scanty tissue. Laparotomy disclosed an unruptured right ovarian mass which contained a chorionic sac with a fetus. The most frequent findings suggesting primary ovarian pregnancy are reviewed.

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Monoamniotic twin pregnancy

A review of the literature and a report of 5 new cases

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MONOAMNIOTIC twin pregnancy is a relatively rare condition which occurs when twins are contained in a single amniotic sac rather than in separate ones.

The purpose of this paper is to review the literature, to point up the increased danger to the fetuses, and to report 5 additional cases of monoamniotic twin pregnancy with 3 double survivals, which have occurred at the Providence Lying-In Hospital during the 11 year period, 1949 to 1959.

History

Quigley[1] states that the first descriptions of this condition appeared in the seventeenth century. These were by Boccalini in 1612, Jakob von Back in 1648, and Viardel in 1671. There was only one description of monoamniotic twin pregnancy in the eighteenth century. Between 1805 and 1903 there were 71 cases collected by Alfieri.[2] In 1935 Quigley reported one case of his own and brought the total in the literature up to 109.

Incidence

Obviously, the true incidence of monoamniotic twin pregnancy cannot be calculated with accuracy unless obstetricians observe all twin deliveries with this possibility in mind and report all such cases.

A study of Table I will show that the ratio of monoamniotic twins to the number of deliveries has been reported as ranging from 1 to 1,000 by King to 1 to 93,000 by Acosta-Sison, quoted by King.[3]

Potter and Crunden,[7] in a review of 332 twin pregnancies occurring at the Chicago Lying-in Hospital between the years 1931 and 1941, found no monoamniotic twin pregnancies.

Wenner[8] in 1956 reported on 100 sets of twins and stated that 4 had monoamniotic placentas. However, Benirschke[9] stated that monoamniotic twinning in man is considered much less frequent and pointed out that Wenner arrived at his figures by a retrospective analysis of records rather than personal examination of the placentas.

During the years of our study at the Providence Lying-In Hospital (Table II) there was one set of monoamniotic twins for every 16,000 deliveries and one set of monoamniotic twins to every 165 twin deliveries.

The figures of Librach and Terrin[6] are significant because over a 2 year period at the Brooklyn Jewish Hospital they personally examined most of the placentas from twin pregnancies. They found one set of monoamniotic twins for every 4,000 deliveries and one set of monoamniotic twins for every 65 twin deliveries.

Further evidence that this condition occurs more frequently than generally reported is King's report in 1952 in which 5 cases were observed in the city of New Orleans within a 5 month period.

The last survey of the literature was made by Craig[10] in 1957. At that time he found total monoamniotic twin pregnancies reported in the literature to be 166 cases.

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Table I. Comparison of incidence of monoamniotic twin pregnancy

Author	*Ratio of monoamniotic twins to deliveries*	*Ratio of monoamniotic twins to twin deliveries*
Ahlefeld[4]	1:16,000	1:169
Aigner (Quoted by Quigley[1])	1: 7,000	
Rosenberg (Quoted by Quigley[1])	1:60,000	
Müller[5]	1: 6,000	
Alfieri[2]		1:256
Acosta-Sison (Quoted by King[3])	1:93,734	1:661
King[3]	1: 1,000	
Librach and Terrin[6]	1: 4,000	1: 65
Providence Lying-In Hospital (1949-1959)	1:16,000	1:165

Table II. Incidence of twins and monoamniotic twins at Providence Lying-In Hospital, 1949-1959

Year	*Deliveries*	*Twins*	*Monoamniotic twins*	*Double survival*
1949	7,000	73	1	1
1950	6,907	70		
1951	7,234	75		
1952	7,344	70	1	1
1953	6,945	80		
1954	5,605	55		
1955	7,791	82		
1956	8,135	84	2	1
1957	7,961	81		
1958	8,264	79	1	
1959	8,175	75		
Total	81,361	824	5	3

Table III. Increase in double survival of monoamniotic twins as reported in the world literature

Author and year	*No. cases*	*Double survivals*	
		No.	*%*
Quigley, 1935	109	17	16
King, 1952	148	30	20
Craig, 1957	166	40	24
Present study, 1959	183	51	28
1935 to 1959	74	34	46

This paper, which includes a survey of the subsequent literature and a report of 5 additional cases, brings the total to 183 cases.

Etiology

Quigley, in his comprehensive review on monoamniotic twin pregnancy, summarized the early theories of etiology as follows: *Primitive unity* held that there was one amnion from the beginning and that the two blastodermic vesicles meet, join, and are enveloped by one amnion. *Primitive duality* stated that each embryo originally contained its own amnion, but somehow the partition between them was broken, resulting in a single amnion.

Coulton, Hertig, and Long[11] in 1947 stated that the type of uniovular twinning is determined by the time at which a fertilized ovum divides. They believed that the inductive force in the formation of the amnion is the presence of the embryo, for no normal ovum has been described with an amniotic sac present before ectoderm and endoderm are already present. The amnion forms between the seventh and the thirteenth day after fertilization. When the split in the germinal disc occurs prior to that time both embryonic plates will form their own amnion, which results in diamniotic monovular twins. When the split in the germinal disc occurs sometime between the seventh and the thirteenth day, monoamniotic monovular twins will result. If the split occurs after the thirteenth day it will be an incomplete one since an axial arrangement has already been formed. This will result in some degree of conjoined monster.

Morison,[12] in discussing the subject of twinning, also pointed out (Fig. 1) that the time at which the cells which yield a monozygotic twin separate from one another determines the variety of monozygotic twin.

For example, when the cells which yield a monozygotic twin separate from one another at the first division or at any stage before the cells destined to form the chorion are defined, each cell mass forms its own chorion. About 25 to 30 per cent of monozygotic twins are born with each twin in its own

separate chorion. Only a detailed comparison, which may be difficult in newborn children and impossible in some that are stillborn, can show these twins to be monozygotic. (Like twins are identical in rigidly determined characteristics; namely, like sex, blood groups, hair, eye color, palm and sole prints.)

Usually, cleavage does not occur until the inner cell mass is enclosed within cells forming the future chorion. Then both twins develop enclosed in a common chorion.

Division of the embryonic area may occur only after the future amnion has begun to form. Then both twins are enclosed in a common amnion as well as in a common chorion. There is a risk at this late stage that separation may not be complete and that a double monster may result. These are always enclosed in a single amnion.

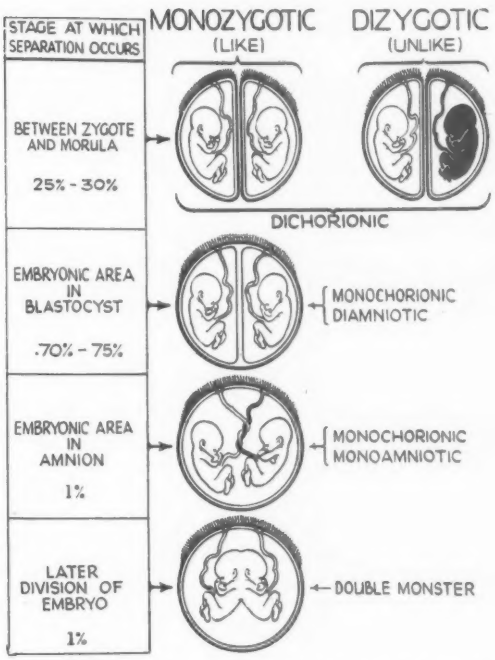


Fig. 1. The different types of twins and how the stage of development at which separation occurs determines the variety of monozygotic twin. Dichorionic twins may be either monozygotic or dizygotic in origin. (From Morison, J. E.: Foetal and Neonatal Pathology, London, 1952, Butterworth & Co., Ltd.)

Clinical significance

It is an accepted fact that multiple births are associated with an increased risk of stillbirth and neonatal death. Morison states that twins are from three to four times more likely to be born dead than are babies of single births. Schatz[13] in the nineteenth century pointed out the hazards of development of one-egg twins. He stated that, because of an anatomical derangement or asymmetry of the vascular system, one of the twins may be robbed of the blood supply necessary for its normal nourishment and functioning, with a resultant progressive weakening of the heart and an accompanying decrease in size. The pressure of the blood from the strong opposite twin comes to bear upon this weakened heart and, if sufficiently strong, overwhelms it and brings its rhythm to a standstill. Newman[14] in 1942 pointed up the hazards of plural birth and stated that there were adequate statistics to show that three to four times as many dizygotic twins and six to seven times as many monozygotic twins are born dead as are single babies and that an even higher proportion die and are aborted before they can be recognized as pregnancies at all.

In monoamniotic twin pregnancies the

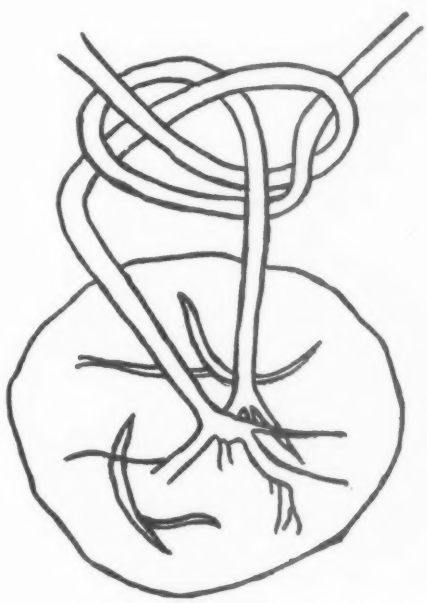


Fig. 2. Obstetrician's drawing of placenta from Case 1, showing intertwining of cords.

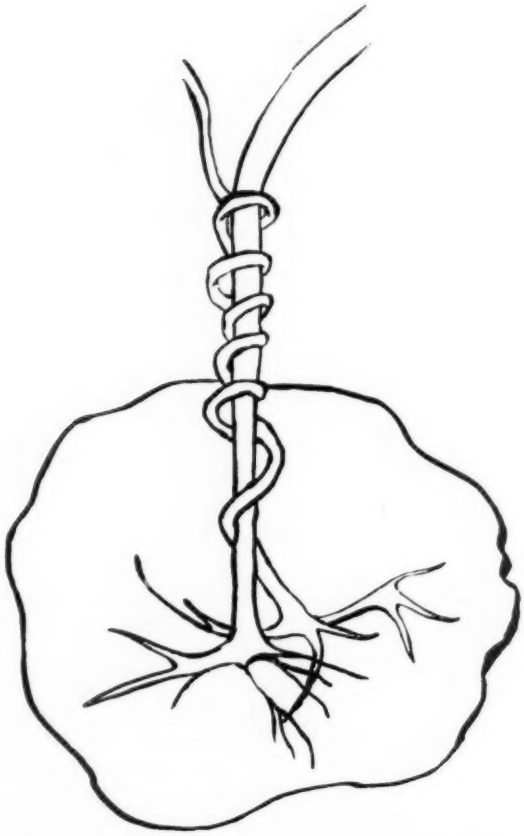


Fig. 3. Obstetrician's drawing of placenta from Case 2, showing one cord twisted around the other six times.

risk is even greater. Quigley reviewed the previous world literature in 1935 and found that the chance of double live birth was only 16 per cent and that the total fetal mortality was 68 per cent. Table III shows that the percentage of double live births has increased since Quigley's report. King in 1952 reported 20 per cent, Craig in 1957 calculated a 24 per cent double survival rate, and the present review finds that the rate is now 28 per cent. Moreover, in the 74 cases of monoamniotic twin pregnancy reported since 1935, there have been 34 double survivals, a 46 per cent rate.

The poor fetal salvage in monoamniotic twin pregnancy is due almost entirely to the interference with fetal circulation coincident to the twisting and knotting of the umbilical cords. Salerno,[15] in a review of the American literature, found the incidence of knotted cords to be 71.4 per cent. However, he felt that this figure might be too high, for twisted cords alert the obstetrician to this condition whereas cases without knotting or twisting may pass unrecognized.

The danger of collision of the twins has been mentioned in the literature, but there are no cases of such reported except by Walters and Whitehead.[16] In their case, both heads were impacted in the pelvis. However, after disengagement of one head, both babies were delivered successfully and survived.

Another possible danger peculiar to this condition is that if the cord of the second twin is around the first twin's neck and cut by the obstetrician, this seriously jeopardizes the second twin unless it is delivered promptly.

Whitehouse,[17] King, and others have mentioned the high incidence of congenital anomalies present in cases of monoamniotic twin pregnancy but stressed the fact that this had no bearing on the high fetal loss. Quigley reported a 10 per cent incidence of monstrosities. Wilson[18] and also Litt and Strauss[19] reported cases in which one twin was anencephalic. These 2 cases are of interest because the factor causing anencephaly here could not be genetic. In the recent literature Semmens[20] reported a case of monoamniotic twin pregnancy in which one twin had congenital heart disease; in 1 of our 5 cases, one of the twins had congenital absence of the tracheal rings.

Case reports

Case 1. Mrs. S. P. was a 30-year-old gravida i, para 0, whose expected date of confinement was January 16, 1949. She went into labor at 4:30 A.M. on Jan. 25, 1949, and was delivered of the first twin at 8:25 P.M. on the same day by a difficult midforceps Scanzoni delivery. It was noted that there was knotting of the cord. The second twin was delivered by low forceps at 8:30 P.M. Both were females; "A" weighed 5 pounds, 12 ounces; "B" weighed 5 pounds, 8 ounces. The babies did well in the hospital and were discharged with the mother.

It was noted that the cords were completely intertwined. The obstetrician's drawing of the placenta is shown in Fig. 2.

Case 2. Mrs. L. B. was a 28-year-old primigravida whose expected date of confinement was Feb. 1, 1953. Findings on general physical examination were normal and the prenatal course was normal. The patient went into labor on Dec. 21, 1952, approximately 6 weeks prematurely. After 18 hours and 20 minutes of labor, she was delivered of premature male twins; "A" weighed 3 pounds, 10 ounces and was delivered at 3:16 P.M.; "B" weighed 2 pounds, 5 ounces and was delivered at 3:18 P.M. It was noted by the obstetrician at the time of birth that there was one placenta and one amnion and that one cord was twisted around the other six times, as shown in Fig. 3. Baby "B" had a thymoma and was treated with x-ray and survived. Baby "A" was found to have congenital absence of the tracheal rings and died at 5 months of age after an unsuccessful operation to prevent recurrent collapse of the trachea. The patient returned to the hospital on Jan. 16, 1953, for curettage because of retained secundines. She has had 2 subsequent normal pregnancies.

Case 3. Mrs. D. T. was a 25-year-old gravida ii, para i, whose expected date of confinement was Feb. 17, 1957. On Sept. 20, 1956, following a period of staining for 2 hours at home, she went into labor and was delivered of female twins at home. She and the twins were then admitted to the hospital. It was noted that the infants' cords were around each other's necks and were knotted, as shown in Fig. 4. Inspection of the placenta revealed the cause for the early miscarriage to be hemorrhagic partial separation.

Pathology report. The first specimen consisted of 2 macerated fetuses of approximately the same size and age with their cords twisted together in a knot. The eyes, ears, nose, and mouth of each were recognizable but were not well formed. The tongue in each could be easily seen. The eyelids were essentially fused although slight touching separated the lids. There was no external evidence of congenital anomalies. The extremities were of the usual conformation and had the usual number of digits with the nails recognizable. The external genitals appeared to be female with a prominent clitoris and a recognizable genital crevice. The sitting height of each was 8 cm. Gross impression was fetal twins of approximately 3 months' gestational age. Also received was a flattened, oval placenta averaging 8.6 cm. in diameter and up to 1.4 cm. in thickness. There was one cavity lined by a smooth and



Fig. 4. Twin fetuses and placenta from Case 3, demonstrating knotting of cords.

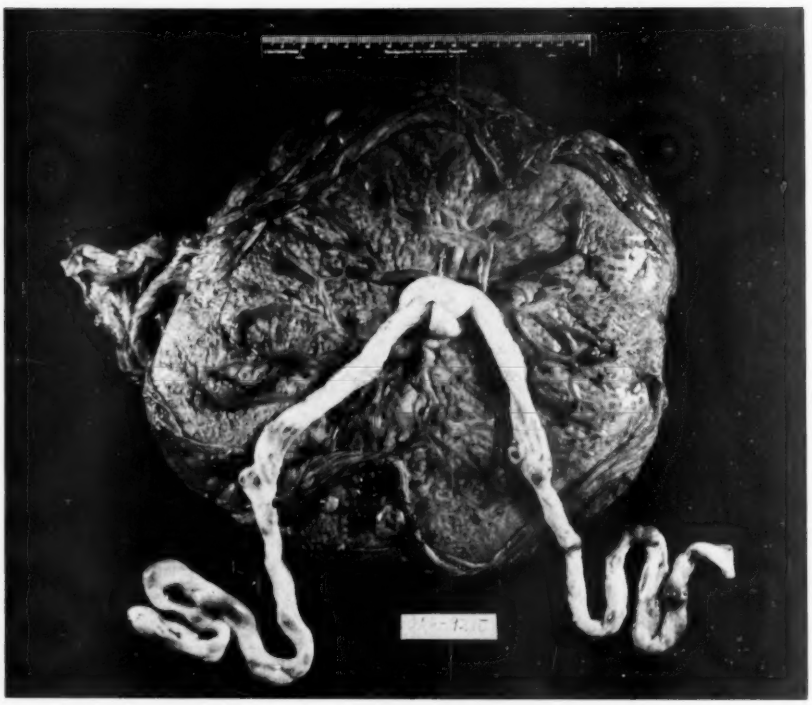


Fig. 5. Placenta from Case 4, showing intertwining of cords.

glistening amniotic membrane from which two separate umbilical cords arose 4.5 cm. apart. One measured 11 cm. and the other 8.1 cm. in length, and they averaged 0.2 cm. in diameter. On the maternal surface of the placenta the cotyledons were small and of the usual number, and there were several areas of increased firmness and yellowing of the tissue. One third of the maternal surface was covered by a moist red blood clot that extended out into an irregular sheetlike piece of moist red clot and friable gray-pink tissue which measured 6 by 5 by 0.3 cm.

Two sections examined under the microscope showed endometrial tissue composed of amniotic membrane and chorionic villi, which are of the immature type. These displayed no significant abnormalities. Rarely, myxomatous degeneration was demonstrable.

Diagnosis. Monoamniotic twin fetuses; immature placental tissue.

Case 4. Mrs. A. C. was a 25-year-old gravida i, para 0, whose expected date of confinement was Oct. 11, 1956. Labor began on Oct. 20, 1956, at 1:00 P.M., and at 5:59 P.M. on the same date she was delivered of a male infant. A knot was noted in the cord at the time of delivery. The second twin was delivered by Scanzoni midforceps at 6:06 P.M. The placenta was delivered 2 minutes later and was noted to be a single placenta with one chorion and one amnion. The total duration of labor was 5 hours, 2 minutes. The babies were identical male twins each weighing 7 pounds, 13 ounces. The babies and their mother were discharged from the hospital in good condition.

Pathology report. The specimen consisted of a large placenta measuring 25 by 22 by 3 cm. with an opened single amniotic sac. Two intertwining umbilical cords were attached centrally to the fetal surface of the placenta (Fig. 5). They measured 52 and 50 cm., respectively, in length and 1.5 cm. each in diameter. Both cords had four nodes; otherwise, they were not remarkable. In addition, on the fetal surface, radial to the cords, were markedly congested blood vessels. The maternal portion showed intact cotyledons which here and there contained an area of fibrosis and calcification measuring from 0.5 to 0.7 cm. in greatest diameter. The pathologist's impression was monoamniotic twin placenta. On microscopy examination, the sections of umbilical cord were not remarkable. Sections of placenta revealed a mature placenta with relatively small villi containing rather large blood-filled

vessels. The villi were surrounded by a single layer of cells. One section showed a focal area of fibrosis of villi.

Case 5. Mrs. E. W. was a 33-year-old white gravida i, para 0, with an expected date of confinement of Nov. 21, 1958. On October 4 she reported to her obstetrician that she had not felt fetal activity for 24 hours. He examined her and fetal heart was unobtainable. She was admitted to the hospital on Oct. 4, 1958, for study because of suspected heart disease. This was not definitely substantiated and she was discharged on October 12. She returned later in the day and was delivered of stillborn twins after 5 hours of labor.

The obstetrician noted after the routine delivery of the first twin by vertex presentation that there was no second amniotic sac present. The second twin was a double footling breech presentation and was delivered routinely. It was noted that the cord of Twin "A" was about the neck of Twin "B" three times and twisted about the cord of Twin "B" four times. The cause of death was contributed to obstruction of circulation in the umbilical cord because of twisting of cords.

Prognosis

There is little or no risk to the mother in this condition. However, as shown by the high fetal mortality, the risk to the fetus is great. Of the 183 total cases in the literature included in this report, there are only 51 cases of survival of both infants (Table IV). Knotted cords do not preclude double live births, as demonstrated by Table V, for, of the 20 cases reported to date in American literature in which both twins survived, 12, or 60 per cent, had knotted cords.

Diagnosis

There is no way to diagnose this condition prior to delivery. At the time of delivery the diagnosis is made by noting the absence of a second amniotic sac and, in some cases, the twisting and knotting of the umbilical cords.

Treatment

At a time when obstetricians are concerned with perinatal mortality more than ever before, it is important that they be aware of this entity so that during each twin delivery, in the absence of a second amniotic sac or when the umbilical cords are intertwined, they will hasten to deliver the second twin.

Summary

1. The literature has been reviewed and 5 additional cases of monoamniotic twinning are reported.

2. The incidence has been discussed and the theories of etiology presented.

3. It has been pointed out that although there is little or no risk to the mother, the hazards to the fetus are great. This is due almost entirely to the knotting and twisting of the cords.

4. An analysis of double survival rates shows that, since Quigley's reported 16 per cent double live births in 1935, there have been 74 cases with 34 double survivals, a 46

Table IV. Cases of monoamniotic twins reported to date in world literature

Author and date	*No. cases*	*Double survivals*
Craig (review), 1957	166	40
Walters and Whitehead, 1957	2	1
Librach and Terrin, 1957	3	3
Roddie,[21] 1957	1	0
Semmens,[20] 1958	1	0
Pickhardt and Breen,[22] 1958	1	1
Salerno, 1959	4	3
Providence Lying-In Hospital, 1959	5	3
Total	183	51

Table V. Cases of monoamniotic twins with double survival reported to date in American literature

Author	*Date*	*No. cases*	*Knotted cords*
Parks and Epstein[23]	1940	1	1
Coulton, Hertig, and Long[11]	1947	2	0
King et al.[3]	1952	2	2
Hagood and Stokes[24]	1953	1	1
Charlton, Winston, and Chomko[25]	1953	2	2
Librach and Terrin[6]	1957	3	1
Craig[10]	1957	1	1
Walters and Whitehead[16]	1957	1	1
Pickhardt and Breen[22]	1958	1	0
Salerno[15]	1959	3	0
Providence Lying-In Hospital	1959	3	3
Total		20	12

per cent rate. This improvement is a reflection of the better facilities for delivery and more skillful obstetrical care.

5. Fetal salvage can be further improved if the obstetrician thinks of this condition during the performance of every twin delivery and, in the absence of a second sac or in the presence of twisted or knotted cords, delivers the second twin without delay.

I wish to thank Dr. Alfred L. Potter, Dr. Edward Cardillo, and Dr. George E. Bowles for permission to include their cases in this report, and Miss Gertrude Cahir for secretarial help.

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Fetal survival in twin delivery

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IN 1954, we published from this institution[1, 2] a study of our experiences with twin deliveries for a 12 year period. Of 41,872 deliveries, 375 were twins. We were interested at that time in evaluating the safety of the various forms of analgesia and anesthesia.

The survey indicated that despite the high incidence of operative obstetrics for both the first and the second twin, the fetal survival with conduction anesthesia was far greater than with inhalation, local, or even no anesthesia. Our over-all fetal mortality was 9.8 per cent, and was 5.4 per cent when conduction analgesia was used, as compared with 14 per cent with general anesthesia and 13.6 per cent with local or no anesthesia. It was felt, in conjunction with Eastman[8] Hingson and Hellman[10] and Lull and Hingson,[12] that conduction anesthesia produced less fetal mortality by virtue of affording relaxation of the birth passages for the deliveries and yet producing no narcotic effects upon the small infant.

The mortality rates in this earlier series were almost equal for the first and second twin. Similar results were obtained by Potter Crunden, Fuller,[15-17] and others, although the majority of reports by such authors as Corston,[6] Munnell and Taylor,[13] Little and Friedman,[11] Guttmacher and Kohl,[9] and others indicate that deaths occur more frequently in the second twin.

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Since our publication, there have been several reports emphasizing the greater hazard of conduction analgesia to infants, as well as the greater fetal mortality of the second twin.[7, 9, 11] It was our clinical impression that our results were more favorable, and, with this in mind, we decided to review our subsequent material. The present study is limited to an analysis of fetal loss, with particular reference to the second twin. Conduction anesthesia remains our choice, and it has been used in 80 per cent of the cases. The effects of anesthesia will not be compared because the 80 per cent incidence of conduction anesthesia would leave any comparison percentages invalid.

Material

During the period from 1953 through 1958 there were 21,790 deliveries, of which 204 were of twins. This comprised an incidence of 0.9 per cent or a ratio of 1 in 106 deliveries. There were no maternal deaths. The maternal complications included 15 cases of toxemia, 3 of which were convulsive, 5 postpartum hemorrhages, 2 cases of abruptio placentae, 2 of placenta previa,

Table I. Per cent mortality by infant weight

Weight (grams)	*First twin*	*Second twin*	*All twins*
Under 1,000	71.4	100.0	85.7
1,000-1,499	54.5	45.4	50.0
1,500-2,500	8.5	6.2	7.3
Over 2,500	2.5	1.4	1.9
Total	10.8	9.8	10.3
Corrected	4.9	3.3	4.1

3 of secondary anemia, 6 of pyelitis, 4 of phlebitis, 2 of endometritis, and one each of diabetes, epilepsy, polyhydramnios and symphysial separation. There were 3 instances of prolapsed cord. The incidence of prematurity (with under 2,500 grams used as the baseline) was identical for the first and second twin—62.7 per cent.

Fetal mortality

In Table I is indicated the over-all twin mortality by fetal weight. In their most recent papers, Little and Friedman[11] and Guttmacher and Kohl[9] exclude antepartum fetal deaths as well as fetuses under 1,500 grams in computing their survival statistics. Accordingly, the mortality for the first twin drops from 10.8 to 4.9 per cent and for the second from 9.8 to 3.3 per cent, while the total twin mortality is corrected from 10.3 to 4.1 per cent. In comparison with the tabulated data drawn from the literature and reported by Little and Friedman and Guttmacher and Kohl, our uncorrected fetal mortality is among the lowest. We continue to observe that contrary to the majority of reports in the literature, our mortality for the second twin, 3.3 per cent, is lower than for the first, 4.9 per cent, instead of being much greater. It has been our contention that the absence of depressing effect of inhalation anesthesia on the second twin, in addition to prompt delivery thereof, exposes the infant to less intrauterine hazard and less respiratory depression, such as occurs with heavy sedation and/or general anesthesia. It is reported that the complete relaxation provided by conduction anesthesia facilitates operative deliveries and reduces the attendant risks of trauma to the newborn.[8, 10, 12, 14]

Method of delivery of twins

Our method of delivery of the first twin does not vary from that of single births. Conduction anesthesia, caudal or saddle, is administered depending upon the stage and character of labor. Those infants presenting by the vertex are delivered in the usual manner, except that we favor the application of forceps to shorten the second stage. The membranes of the second twin are then ruptured and delivery accomplished spontaneously, or by operative procedures, to obtain a minimal delay. Breech extraction and version and extraction procedures are performed without supplemental anesthesia, except in rare instances, in the interval between contractions. Our incidence of operative procedures is 82.8 per cent. In the first twin it is 80.9 per cent, and in the second it is 85.8 per cent. This is summarized in Table II. Spontaneous vertex and breech deliveries are infrequent in both the first and second twin as compared to forceps, breech extraction, and version and extraction. The latter has an incidence of 21.1 per cent, which is considerably higher than is reported in the literature; the mortality rate is comparable.

Of the 7 cesarean sections the indications were previous cesarean section in 5, cephalopelvic disproportion in one, and previous myomectomy in one.

Table II. Method of delivery of twins

Method of delivery	*First twin*		*Second twin*		*All twins*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Spontaneous vertex	39	19.1	29	14.2	68	16.7
Low forceps	94	46.1	26	12.8	120	29.4
Midforceps	32	15.7	19	9.3	51	12.5
Spontaneous breech	4	2.0	2	1.0	6	1.5
Breech extraction	28	13.7	78	38.2	106	26.0
Version and extraction	0	0	43	21.1	43	10.5
Cesarean section	7	3.4	7	3.4	14	3.4
Total	204	100.0	204	100.0	408	100.0
Operative rate	80.9%		85.8%		82.8%	

Table III. Per cent twin mortality by infant weight and method of delivery

Weight (grams)	Spontaneous vertex		Low forceps		Midforceps		Spontaneous breech		Breech extraction		Version and extraction		Cesarean section	
	First twin	Second twin	First twin	Second twin	First twin	Second twin	First twin	Second twin	First twin	Second twin	First twin	Second twin	First twin	Second twin
Under 1,000	80	100	–	–	–	–	0.0	–	100	100	–	100	–	–
1,000-1,499	40	–	50	–	66.7	–	–	–	–	33.3	–	–	100	100
1,500-2,499	5.9	0.0	3.9	0.0	0.0	0.0	50	0.0	22.2	10.5	–	10.3	25	0.0
Over 2,500	0.0	0.0	2.4	0.0	0.0	0.0	0.0	–	10.0	0.0	–	7.7	0	0.0
Total	17.9	10.3	4.3	0.0	6.2	0	25	0	21.4	12.8	–	11.6	28.5	28.5

Fetal mortality by method of delivery

Table III is an analysis of fetal death by weight and method of delivery. It is striking to note that when either twin presents by other than vertex, the fetal mortality mounts rapidly. This is particularly notable in the premature group and, although the mortality rate diminishes in the heavier babies, there is still a preponderant loss in other than vertex deliveries. Even when the correction factors previously noted are applied (Table IV) the same relationship exists.

Table IV. Per cent twin mortality by weight and method of delivery (eliminating under 1,500 grams and antepartum deaths)

Method of delivery	First twin	Second twin	All twins
Spontaneous vertex	0.0	0.0	0.0
Low forceps	3.2	0.0	2.5
Midforceps	0.0	0.0	0.0
Spontaneous breech	33.3	0.0	20.0
Breech extraction	15.4	6.1	8.7
Version and breech extraction	0.0	9.5	9.5
Cesarean section	16.7	0.0	9.1
Total	4.9	3.3	4.1

Fetal loss by presentation

Table V emphasizes the difficulties for both babies when presentation and delivery are by other than vertex. Excluded from this analysis are the 14 babies delivered by cesarean section in addition to the previous correction factors. Although the fetal loss by presentation for each baby is 3.9 per cent, the first twin suffers the major portion of this loss when it presents by other than vertex, whereas the loss in the second twin is exclusively when it presents by breech or when it is delivered by version and extraction. These findings are basically similar to those reported by Little and Friedman[11] and Guttmacher and Kohl.[9]

It seems, therefore, that the time-honored procedure of performing elective podalic version and extraction of the second twin might very well be replaced by operative procedures which would effect the delivery of the second twin by vertex.

Comment

The incidence of antepartum deaths in twins is perhaps no greater than in single pregnancies, so that it is with labor and delivery that difficulty ensues. Furthermore, the mortality resides in the babies weighing under 2,500 grams, the larger ones apparently suffering no greater risk than those of

Table V. Fetal loss by presentation at delivery

Presentation	First twin		Second twin	
	No.	% mortality	No.	% mortality
Vertex-vertex	62	4.8	66	0.0
Vertex-breech	63	1.6	58	1.1
Vertex-version and extraction	27	0.0	29	1.7
Breech-vertex	4	0.0	4	0.0
Breech-version and extraction	12	8.3	12	0.0
Breech-breech	10	20.0	11	1.1
Total	178	3.9	180	3.9

single pregnancies.[14] Therefore, the conduct of labor and the methods of delivery with respect to facility, minimum trauma, anesthesia, and delay between the births of the first and second twin are the chief factors to be considered. Prematurity cannot be eliminated but has been slightly reduced as a result of improved prenatal care. Prolonged bed rest to prevent premature onset of labor as prescribed by Bender[5] is not practical. Potter[15] states that improvements in postnatal care will contribute to reduction of mortality rates among premature infants where postnatal asphyxia is the leading cause of death.

Respiratory center depression may occur in utero and is augmented by inhalation anesthesia and trauma through the birth passages. When conduction anesthesia is used, labor continues normally with no alteration in maternal vital signs or placental exchange, and the birth passages remain relaxed, offering minimum obstruction to the descending fetus or to operative procedures. The fetus thus cries and breathes spontaneously within a very short period of time. Since all authors—Eastman,[8] Hingson and Hellman,[10] and others—favor it for premature babies, its application in twin deliveries with its increased incidence of prematurity is to be encouraged, and it appears to be accepted on the basis of our continued lesser fetal loss in the second twin.

Summary

1. The most significant single factor in fetal mortality in twin deliveries is that of prematurity.

2. Conduction anesthesia alters fetal physiology the least and also affords greater pelvic relaxation for operative deliveries, thus increasing fetal survival.

3. We continue to observe that there is no increase in fetal loss of the second twin and that actually the reverse is true.

4. In our series fetal death of the second twin occurred only when the infant was delivered by the breech or after version and breech extraction.

5. It is suggested that we consider the feasibility of delivering the second twin by the vertex and attempt to accomplish cephalic rather than podalic version whenever possible.

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Effect of estriol on breast engorgement and lactation in nonnursing mothers

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Doisy and associates[1] and Marrian[2] were the first to isolate estriol. They found it in urine from pregnant women. With but few exceptions estriol has been isolated only from human material and has therefore been considered specific to human beings. It has been generally regarded as the end product and excretory form of estrogen metabolism. Its effect in certain biologic assays such as in the vaginal cornification test according to Allen-Doisy is weak. Curtis and Doisy,[3] however, showed that in the vaginal opening test estriol had a stronger effect than estradiol, yet its significance as an estrogen substance in the organism has received little attention.

Investigations by Puck and associates[4-8] and others[9-11] have nevertheless shown estriol to possess certain interesting properties. Estriol has a strong and readily demonstrable effect on the vulva, vagina, and uterine cervix, while its effect on the uterine corpus and the endometrium is much weaker.[6, 9] Knowledge of these effects has resulted in increased interest in estriol which is now being used more and more in gynecology. Puck[4] thus successfully treated such diseases as pruritus vulvae, colpitis, cervicitis, dysmenorrhea, and the menopausal syndrome with estriol. Estriol has also proved useful in the pre- and postoperative treatment of patients with uterine prolapse and in association with other vaginal operations on women in the menopause.[11] Estriol does not produce uterine bleeding unless used in large doses for a long time. Another advantage is that estriol can be given throughout the entire menstrual cycle without interfering with ovulation or menstruation. It appears to differ from other estrogenic substances in so far as it presumably does not inhibit hypophyseal function.

The effect of estriol on the mammary gland has hitherto not been studied. It has been shown in rats that estriol interferes with lactation.[12] In a preliminary examination[13] of a small amount of material it has been shown that estriol reduces the postpartum breast symptoms in nonlactating parturients and after late abortion. That material has now been extended and the effect of estriol studied in greater detail.

Material

The material consisted of 135 women treated, 84 after parturition at full term or almost full term (Group I) and the remaining 51 after spontaneous or legal abortion in the fourth to the seventh month (Group II). In Group I lactation was not desired, either because the child had died or because the mother had had the child adopted. Group II is summarized in Table I.

The dose of estriol used varied somewhat during the period covered by the investigation. In the beginning the dose used was 5 mg. intramuscularly daily for 4 to 5 days but was gradually diminished to oral treatment with tablets of 0.25 mg., 4 tablets daily for 4 to 6 days. Estriol is relatively more

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Table I. Survey of patients treated with estriol (Group II)

Abortion in month of pregnancy	*No. of legal abortions*	*No. of spontaneous abortions*	*Total*
4	9	3	12
5	25	7	32
6	3	2	5
7	–	2	2
	37	14	51

effective per os than estradiol and other natural estrogens, probably because of its higher solubility in water. The first injection or tablet was given immediately after parturition in Group I or as soon as treatment was indicated, often within the first day, since it is known that early treatment is much more effective than late. Breast symptoms are common but by no means regular after late abortion; therefore, the women in that group did not receive estriol until they complained of tension and tenderness or until milk secretion had commenced. The women received no other treatment except a supporting brassière.

It is difficult to evaluate the effect of therapy. In the present investigation is was judged by the opinion of the patients of their symptoms. Most patients were interviewed 3 to 4 weeks after they had left the hospital and were then questioned regarding any late symptoms and recurrences. The effect of treatment was said to be good if the symptoms had completely disappeared or if they had become negligible and disappeared within a few days. The effect was said to be moderate if the symptoms had appeared despite treatment but disappeared within a few days. In Group II, where therapy was not started until the symptoms had appeared, the effect was classified as moderate if the symptoms had persisted for several days or become fairly severe. The effect was said to be poor if the symptoms continued to be really troublesome for a long time, if they recurred, if milk secretion started, or if other therapy had proved necessary.

As known, these postpartum or postabortal breast symptoms are sometimes only trivial and require no treatment. According to King[14] only about half of all patients receiving no treatment have any trouble and this number can be reduced with placebo to about 25 to 30 per cent. The result of any treatment of these symptoms, both therapeutic and prophylactic, must therefore be evaluated with caution. We have previously treated these symptoms somewhat differently, usually with ethinyl estradiol (0.05 mg. five times daily for 5 to 6 days), androgen (testosterone propionate 100 mg. intramuscularly once or twice), or in combination estrogen and progesterone (20 mg. progesterone plus 2 mg. estradiol benzoate intramuscularly two to three times).

The effect of estriol therapy was compared with the results of earlier preparations.[15-17]

No side effects ascribable to estriol therapy were observed. All of the patients tolerated the preparation well and in none was it necessary to interrupt treatment. No late complications in the form of poor involution of the uterus or uterine bleeding were noted.

Results

The results of treatment are given in Tables II and III.

In Group I, which consists of 84 patients delivered at or near full term the effect was classified as good in 72, as moderate in 11, and as poor in 1. In about 86 per cent, then, the effect was good. In Group II which consists of women with late abortions, the effect was somewhat better, probably because the symptoms were less severe. Of the 51 women in this group 47 described the effect as good, 3 as moderately good, and 1 as poor. In this group, then, the number of patients in whom the preparation produced a good effect was about 92 per cent. Of the entire 135 patients, the effect was good in 119, or 88 per cent. Oral treatment appeared to have the same effect as injection treatment (in the total material 85 per cent reported a good effect of oral treatment, 8[illegible] per cent of intramuscular treatment). In the 2 cases in which the effect was described

as poor it was necessary to resort to other therapy (ethinyl estradiol) in one and in the other the symptoms disappeared after repeated treatment with estriol.

Comment

The physiology of lactation is not properly understood. During pregnancy the mammary glands develop but the secretion of milk is prevented probably by the large amounts of estrogen and progesterone produced in the placenta. It is assumed[18] either that these hormones prevent the release of prolactin from the hypophysis or that the mammary gland is refractory to prolactin. After parturition, when the estrogen and progesterone titers rapidly fall, this inhibition disappears and lactation starts after a period of increased lymphatic and venous stasis. In this period the patient has the well-known symptoms of tension, tenderness, and heaviness of the breasts.

To inhibit these symptoms or lactation, hormone therapy has been employed since their availability for clinical use. They have been tried by themselves or in combination. New combinations of sex hormones and new derivatives and substances with a similar effect have been investigated. The results have been judged as varying from almost 100 per cent effect to no effect at all.[17] Broadly speaking, it is, however, obvious that both estrogens and androgens, possibly in combination with progesterone, have a reliable effect on the breast symptoms after parturition.

The underlying mechanism of the effect of these preparations is, however, still ob-

Table II. Results of estriol treatment in Group I, patients delivered at or near term

	Estriol therapy				*Effect*			
No. of cases	*Method of administration*	*Daily dosage (mg.)*	*No. of days*	*Total dosage*	*Good*	*Moderate*	*Poor*	*Per cent good*
31	Intramuscular	5	3-5	15-25	27	4	0	87
10	Intramuscular	3	3-4	9-12	9	1	0	90
20	Intramuscular	1	3-5	3-5	17	3	0	85
23	Oral	1	4-6	4-6	19	3	1	83
84					72	11	1	86

Table III. Results of estriol treatment in Group II, cases of abortion in fourth to seventh month

	Estriol therapy				*Effect*			
No. of cases	*Method of administration*	*Daily dosage (mg.)*	*No. of days*	*Total dosage*	*Good*	*Moderate*	*Poor*	*Per cent good*
16	Intramuscular	5	3-5	15-25	15	1	0	94
6	Intramuscular	3	3-4	9-12	6	0	0	100
18	Intramuscular	1	3-5	3-5	16	1	1	89
11	Oral	1	4-6	4-6	10	1	0	91
51					47	3	1	92

scure. Investigations in this field have been carried out largely on animals and the results vary with the type of animal used. Estrogens probably have two sites of attack. They inhibit the hypophysis and the release of the prolactin, and probably the doses used have a local effect on the mammary gland and surrounding tissue. This local effect may consist partly in rendering the gland refractory to different stimuli, and the estrogens may, by decreasing lymphatic and venous stasis, also give the patient relief. It is true that it has been claimed that this local effect cannot be achieved in hypophysectomized experimental animals[19] and that it must thus be dependent on an intact hypophysis. The effect of estrogen should then be due to a direct or indirect action on the hypophysis.

The effect of estriol can be compared to that achieved with other sex hormone therapy. It is therefore logical to assume that estriol acts upon the mammary gland and surrounding tissues in the same way as other estrogens.

From a clinical point of view, estriol offers no advantages over other preparations. It can, however, be administered orally; injections are unnecessary, it produces no side effects, and it involves no risk of uterine bleeding or subinvolution of uterus.

Summary

1. Estriol had a good effect on postpartum and postabortal breast symptoms in 80 to 90 per cent of nonnursing parturients treated.

2. Oral administration gave as good results as parenteral administration.

3. In the doses used estriol produced no side effects, and its clinical value is discussed.

4. It might be concluded that estriol has the same effect as other estrogens on breast engorgement. The effect is probably transmitted via the hypophysis so that estriol, in contrast to what has hitherto been believed, probably has an inhibitory effect on the hypophysis. The possibility of this effect depending partly or entirely on a local effect on the mammary gland and surrounding tissue is discussed.

Estriol was courteously supplied as Ovesterin by A/B Pharmacia, Uppsala, Sweden.

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Suppression of postpartum lactation and prevention of breast engorgement in nonnursing mothers

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IT HAS been well established that large doses of either androgens or estrogens are effective in inhibiting postpartum breast engorgement and suppressing lactation.[1-5] However, the usefulness of single hormones for this purpose has been limited because of undesirable manifestations which include secondary breast engorgement, persistence of lochia, withdrawal bleeding, and excessive delay in the resumption of normal menstrual cycles. An ideal agent for suppression of lactation and prevention of breast engorgement must possess the following: (1) effectiveness, (2) ease of administration, (3) freedom from unwanted effects, and (4) low cost. In the past, no single hormone preparation has met all of these requirements.

In order to decrease the undesirable effects of single hormones, combinations of androgens and estrogens have been developed. Such preparations have been demonstrated to be effective in inhibiting postpartum lactation and breast engorgement in nonnursing mothers and have been shown to have fewer undesirable side effects.[6-8] The previously available preparations of combined hormones (oral or injectable), however, have necessitated daily administration to be effective and hence still failed to meet the "ease of administration" requirement for an ideal agent.

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Recently, an androgen-estrogen combination of the long-acting steroid esters, testosterone enanthate and estradiol valerate,* has become available which from the initial reports[9-14] appears to fulfill the requirements listed above. The purpose of this study was to evaluate further the effectiveness of this combination of steroids in controlling postpartum breast manifestations and lactation. The initial portion of the investigation was carried out as a double-blind evaluation of the dose relationship. The second portion of the study was performed to determine the effect of an increased dosage.

Plan of study

Identical-appearing solutions, one consisting of 90 mg. of testosterone enanthate with 4 mg. of estradiol valerate per milliliter dissolved in sesame oil with 0.5 per cent chlorobutanol as a preservative, and the other consisting of merely the sesame oil vehicle without steroid components, were prepared in 4 ml. vials. These were stored at room temperature throughout the study. These solutions were administered intramuscularly as single injections through a 20 gauge needle, either in the buttock or the arm, as soon as feasible after delivery in the first 100 cases and immediately following the third stage of labor in 52 subsequent cases.

All patients were questioned during the

*Supplied as Deladumone by Dr. Edward C. Riefenstein, Associate Medical Director, E. R. Squibb & Sons, New York.

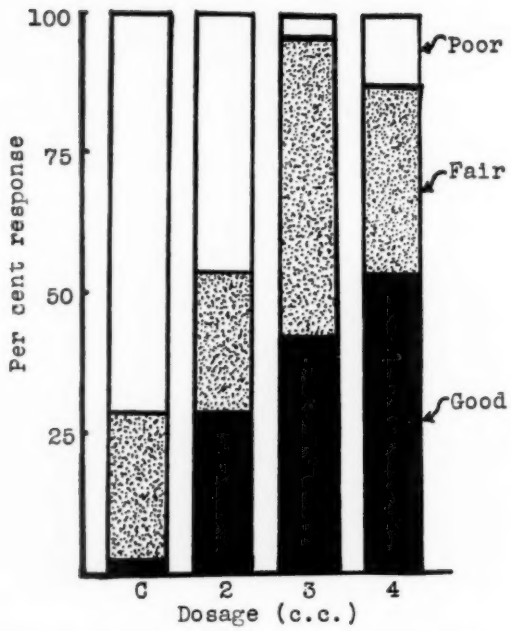


Fig. 1. Per cent response to Deladumone. *C* = control; *2, 3, 4* = cubic centimeters of Deladumone.

last trimester of their pregnancies to ascertain their desires concerning breast feeding, and most of those who were undecided were encouraged to nurse their infants. The patients were questioned again on admission to the hospital in labor, and those women who did not desire to breast feed were included in the study. The steroid preparation and the control substance were given alternately without the patients' being told the nature of the injection. The preparations were administered from vials marked with code numbers, the meanings of which were unknown to the nurses who gave the injections; 49 patients received 2 ml. and 51 patients 3 ml. of the unknown preparations. After the initial portion of the investigation had been completed and analyzed, an additional 52 patients were given 4 ml. of a known preparation of testosterone enanthate and estradiol valerate.

A study sheet was attached to the chart of each patient and was marked at the top with the patient's name, the code number of the preparation, and selected obstetrical information including the history of previous breast engorgement, lactation, and parity. Observations on these patients were carried out on admission and at 2, 4, and 6 days post partum, as well as at the 6 weeks' postpartum visit, by an attending physician, a resident, or an intern. Since there is no standard of measurable end points, a grading criteria was agreed upon by all observers prior to institution of the study. These ranged from 0 to 4+ in the following categories: lactation, palpable tenderness, palpable engorgement, and fever. Whenever possible, two examiners saw the patient in order to reduce the individual variation in the grading status. The code of the medications was not known to the investigators until this portion of the study had been completed and the results had been analyzed.

At the 6 weeks' postpartum visit, the patients were questioned concerning the over-all effectiveness of the preparation, the duration and the amount of the lochia that had been experienced (especially in relation to previous pregnancies), the onset of normal cyclic menstrual function, and the occurrence of any untoward reactions. In addition to these examinations, the Home Nursing Service personnel visited as many as the patients as possible on the tenth day after discharge from the hospital, questioned the patients on the same points and examined them for the previously mentioned findings. Home Nursing Service visits were made on 84 per cent of the patients. The majority of the remaining women who were not observed during the postpartum period had been returned to their local referring physicians, who had been asked at the time of discharge from the hospital to inform the author of any postpartum difficulties. None of the local physicians contacted the author with such problems.

When the results of the first portion had been analyzed, a second series of 52 women were treated with one injection of 4 ml. of testosterone enanthate and estradiol valerate immediately following the third stage of labor to evaluate the effect of one injection of an increased amount of the hormone preparation. Of the 152 patients initially

included in the study, the data on 5 women were discarded because inadequate information was available for evaluation. One of these was from the 2 ml. hormone group and 4 from the 4 ml. hormone group. This accounted for 4 per cent of the 2 ml. group and 7.7 per cent of the 4 ml. group. The discard rate in the 4 ml. group is higher than is desirable in a study of this kind.

The results were grouped in three categories: a good response, a fair response, and a poor response. A good response was one in which there was no more than a 1-plus degree of lactation limited to one day of examination, not more than a 1-plus degree of engorgement, a 1-plus degree of tenderness, and no fever. A fair response was defined as not more than a 2-plus degree of lactation on any one day, a 2-plus degree of engorgement, and/or a 2-plus degree of tenderness, and no evidence of fever. A poor response was defined as one in which any of the categories was in excess of these limits or in which the patient developed postpartum breast engorgement or any other significant untoward reaction.

Results

The results are given in Table I, which is self-explanatory. This indicates a more favorable response to the larger (3 ml.) dose of testosterone enanthate and estradiol valerate. An additional series of 52 women were given a single injection of 4 ml. of this preparation. With this dosage, 26 patients (54 per cent) had a good response, 16 patients (33 per cent) had a fair response, and 6 (13 per cent) a poor response. Thus, the increased amount of the hormone preparation that was injected was associated with a still greater increase in the number of patients who obtained a good response. The results indicate, therefore, that when either 3 or 4 ml. of the hormone is injected, a fair to a good relief of symptoms may occur in approximately 90 per cent of patients.

Undesirable manifestations

No serious pharmacologic or mechanical difficulties were encountered with the placebo or the drug. The minor problems, questionably related to the hormone, included some prolongation of the time during which lochia was present and some delayed breast engorgement. The exact incidence of these undesirable manifestations was difficult to determine accurately since much of the evaluation had to be based on the patient's impression. However, no patient re-

Table I. Data for individual dosage levels

	Control groups				*Deladumone groups*					
	*2 ml.**		*3 ml.**		*2 ml.**		*3 ml.**		*4 ml.†*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
A. Response to injection										
Good	0	0	1	4	7	29	10	42	26	54
Fair	5	21	8	30	6	25	13	54	16	33
Total	5	21	9	34	13	54	23	96	42	87
Poor	19	79	18	66	11	46	1	4	6	13
Total cases analyzed	24		27		24		24		48	
Discarded cases‡	0		0		1	4	0		4	7.7
Total cases injected	24		27		25		24		52	
B. Undesirable effects										
Prolonged lochia	2	8.3	1	3.7	3	12.5	2	8.3	2	4.2
Delayed breast engorgement	6	25	5	18.5	4	16.6	4	16.6	6§	12.5

*Administered as a coded unknown preparation.
†Administered as a preparation known to be Deladumone.
‡Inadequate information available for evaluation.
§Initial response good in 2 of the cases with delayed breast engorgement.

quired treatment or curettage for blood loss. Of the 51 women who received either 2 or 3 ml. of the placebo preparation, 3 patients (5.8 per cent) had prolonged lochia and 11 (21.6 per cent) had delayed breast engorgement. Similarly, 5 patients (10.4 per cent) had prolonged lochia and 8 (16.6 per cent) had delayed breast engorgement in the group of 48 women who were given either 2 or 3 ml. of the hormones; only 2 patients (4.2 per cent) had prolonged lochia, and 6 patients (12.5 per cent) had delayed breast engorgement in the group of 52 women who were given 4 ml. of the hormones.

Three patients mentioned local reactions of varying severity with localized dermatitis. All of these had been given the 4 ml. dosage. In 2 cases this was a source of real discomfort to the patient. Tenderness over the site of the injection was not a problem with the great majority of the patients; however, some did complain of slight localized discomfort for short periods of time. There were no technical problems with the actual administration of the drug. Once the routine had become established, the nursing staff found no inconvenience in its administration, and it did not interfere in any way with the delivery procedure.

Comment

Analysis of the results of this investigation indicates the effectiveness of testosterone enanthate and estradiol valerate in preventing postpartum breast engorgement and suppressing lactation in nonnursing mothers as determined in a double-blind study. No significant undesirable manifestations were noted. Clinical impression seems to indicate the importance of administration of the preparation promptly at the end of the third stage of labor or actually prior to the completion of the delivery. One patient went on to breast feed her infant in spite of the hormone administration. The patient had a very easy adjustment to breast feeding with minimal breast engorgement and satisfactory lactation. This illustrates the well-recognized fact that lactation cannot be inhibited completely in mothers who do nurse in spite of hormone therapy.

It should be noted that the prolongation of lochia and delayed breast engorgement which were observed in this investigation may not have been induced by the administration of the hormone preparation, since the incidence of these manifestations was not less in the women who received merely an injection of the placebo preparation. If a control series had not been included in this study, these unwanted effects might have been interpreted as undesirable effects of the hormone combination.

It must be stated here that Dr. John Mithoefer, a consultant in statistics who kindly reviewed our work, critized some aspects of the investigational design. Bias should have been eliminated as a determinant of the results by assigning the steroid or the control substance to the patients in random order rather than alternately. Because of this error in design the results cannot be attributed to a drug effect within a known degree of confidence nor can the results be meaningfully subjected to tests of statistical significance. Nevertheless, I feel it is of value to report our experience with this drug.

Summary

1. A double-blind study of 100 women was undertaken to determine the efficacy of the administration of one injection (2 or 3 ml.) of testosterone enanthate and estradiol valerate in preventing postpartum lactation and breast engorgement in nonnursing mothers.

2. An additional 52 patients were added to the original study to determine the effect of an increased dose (4 ml.) and of a more prompt administration (immediately following the third stage of labor) of testosterone enanthate and estradiol valerate in controlling the postpartum breast manifestations.

3. This drug is an effective agent for inhibiting postpartum lactation and breast engorgement in nonnursing mothers.

4. The only undesirable manifestation

following the intramuscular administration of this hormone preparation appeared to be a localized reaction to the preparation, and this occurred only in the 4 ml. dosage.

5. One single injection of either 3 or 4 ml. of testosterone enanthate and estradiol valerate appeared to be an adequate dose for satisfactory control of breast engorgement and lactation in approximately 90 per cent of nonnursing postpartum women.

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Anti-inflammatory drugs in obstetrics and gynecology

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IN ORDER to relieve discomfort from pain in the perineal region following delivery and vaginal plastic procedures, many forms of therapy have been used. Such treatment consisted of various types of analgesic sprays, the application of wet or dry heat and the administration of narcotics. Although these remedies helped, they were limited in scope inasmuch as they offered temporary relief of symptoms but were not therapeutically consistent in relieving causative factors. Consequently, the results were effective only as long as the local treatment was continued. In abdominal cases, as well as in patients who have perineal wounds, the local discomfort is probably due to the inflammatory reaction as a result of operative trauma.[4] It seems logical, therefore, that some type of treatment should be directed toward the alleviation of edema, cellular infiltration, and the promotion of healing.

In 1957 and 1958 Miller[8] and Kremer[7] were able to demonstrate that reaction to inflammation in infection and surgical diseases was not necessarily a favorable phenomenon. They proved that a patient's convalescence was speeded and enhanced by eliminating or modifying edema, erythema, and local cell infiltration with the use of anti-inflammatory drugs. The various factors that are associated with inflammatory reactions are not entirely understood. The increase in capillary permeability, fibrin plugging venules and lymphatics with resultant swelling, seems responsible for the lack of response to antibiotic agents. These conditions are held responsible for the constant devitalization of the surface tissue elements, thereby providing media for the further growth of bacteria. This work was applied clinically to a variety of surgical patients by Connell and Rousselot.[3] Five anti-inflammatory drugs were used in their study. Streptokinase, trypsin, cortisone, hydrocortone, and phenylbutazone* were tried; of this group phenylbutazone was found to be the most effective.[4]

Phenylbutazone possesses well recognized analgesic and anti-inflammatory properties. This drug is a pyrazolidine derivative with the following formula: 1-2 diphenyl-4 butyl-3-5 pyrazolidinedione, a product closely allied to the amidopyrenes.[10] While it was first used extensively in the treatment of rheumatoid arthritis, it fell into disrepute because of its deleterious effects upon the hemopoietic system. With more judicious usage of the drug, however, these effects have been minimized.[4] The drug is contraindicated if there is edema, cardiac decompensation, a history of peptic ulcer or drug allergy, hypertension, and renal, car-

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*Butazolidin, Geigy Pharmaceuticals, Yonkers, New York

diac, or hepatic damage. Stein and Rose[9] demonstrated the merit of phenylbutazone in the treatment of superficial thrombophlebitis. Because of the gratifying results demonstrated in this disease Archambault and Archambault[1] felt that the same results could be obtained in patients suffering from hemorrhoids in the acute stage. This drug had no lytic effect upon thrombosis but has brought about relief from pain and edema in 95 per cent of their cases. Connell and Rousselot[4] reported the same type of analgesic and anti-inflammatory action in patients with ulceration, surgical wounds, cellulitis, and abscess formation. With this information in mind, it was felt that these drugs, even without the use of antibiotics, could be equally effective in the relief of postoperative discomfort experienced by gynecologic and obstetric cases.

Pilot study

This report is concerned with a pilot study of 120 patients treated with phenylbutazone in the postpartum and postoperative period (Table I). In addition 299 patients were evaluated in a three way double-blind study using phenylbutazone, compound G27202,* now known as oxyphenbutazone, and a placebo. The results of that survey will be given in detail later.

In the initial study of 120 cases, 99 were obstetric patients, 94 of whom were delivered vaginally and 5 of whom had cesarean sections. In the gynecologic group there were 15 patients who were treated by total abdominal hysterectomy; one had a Marchetti procedure, 3 had vaginal hysterectomies, and 2 had abdominal laparotomies for the purpose of ligating the Fallopian tubes.

The drug was given to all of the patients in the following manner: the medication was started as soon as nausea from the anesthetic agents had ceased. For the first 3 days 200 mg. of phenylbutazone was administered three times daily with meals. On the following 4 days, if hospitalization was prolonged to that point, the dosage was reduced to 200 mg. twice daily. No patient received more than the maximum dose of 3,400 mg. In the routine vaginal delivery this was decreased to 2,600 mg. since the hospital stay was 5 days. Narcotics were withheld unless specifically needed, and then were ordered in individual doses. The salt intake was restricted because of the salt and water retention properties of the drug itself, and each patient was watched closely for evidence of side reactions, such as skin eruption and the signs and symptoms of peptic ulcer. The appraisal of this treatment was made from the standpoint of pain relief, narcotic withdrawal, local inflammatory reaction, and the type and degree of any side reaction. Due to the reported toxicity of phenylbutazone, we were skeptical of its use. However, upon extensive investigation of the literature and the experiences of others, it became apparent that the drug was comparatively safe if used in small doses over a short period of time.[1, 4] We, therefore, adhered to the same dosage schedule advocated by the other workers and limited its administration to hospitalized patients.[1, 4] Excluded from this study were cases in which there was evidence of hypertension, renal or cardiac disease, or marked edema.

Since pain is a subjective phenomenon and difficult to evaluate, a system had to be evolved in order to arrive at significant conclusions. In a daily interview these patients were asked two questions: (1) "How do you feel; do you have any complaints?" (2) "Do your 'stitches' or incision bother you?" By a searching review of the answers, favorable and unfavorable results in regard to pain relief could be determined. These were classified as excellent, good, fair, and poor. The term "excellent" indicated a negative answer to both questions, no need for narcotics except in rare instances, and no evidence of inflammatory reaction around the surgical wound. The term "good" designated that there was slight discomfort which required only 2 or 3 doses of narcotics and no evidence of inflammation. The term "fair" was used to classify

*Geigy Pharmaceuticals, Yonkers, New York.

Table I. Pilot study with phenylbutazone

Type of patient	*No. patients*	*Side effects*	*Result*			
			Excellent	*Good*	*Fair*	*Poor*
Obstetric vaginal delivery	94	2 urticaria	58	24	11	1
Obstetric cesarean section	5	None	5	0	0	0
Gynecologic hysterectomy	15	1 nausea	14	1	0	0
Gynecologic Marchetti operation	1	None	1	0	0	0
Gynecologic cornual resection	2	1 papular eruption	1	1	0	0
Gynecologic vaginal hysterectomy	3	None	3	0	0	0

those patients who complained of moderate to severe pain, required repeated doses of narcotics, and exhibited no inflammatory reaction. The term "poor" described those patients who had no relief of pain, and, in the obstetric cases, needed additional therapy such as compresses, sprays, sitz baths, and larger doses of narcotics; however, there was still no evidence of edema or inflammation.

In the gynecologic cases, 19 patients had excellent relief from pain while the remaining 2 were rated as good. The 94 obstetric patients who had vaginal deliveries and the 5 who had abdominal sections responded in the following manner: excellent relief from pain in 63, good relief in 24, fair relief in 11, and no relief whatever in one. All of the patients in the various groups were unaware that anything other than the usual drugs were given during the postpartum or postoperative care. The narcotic preparations were withheld and ordered only as the need arose. The 21 gynecologic patients received three doses of Pantopon in the first 36 hours. After this period of time they were comfortable and no further pain-relieving medication was necessary. The 5 patients with abdominal deliveries were each given three 20 mg. doses of Pantopon during the first 24 hours. No other narcotics were necessary for the duration of their 8 day hospitalization. Of the 94 patients who had vaginal deliveries with episiotomies, 50 had one dose of codeine, 32 mg., in the first 24 hours post partum. Further narcotic pain-relieving drugs were unnecessary for the remainder of their hospital stay.

Table II. Double-blind study on phenylbutazone and G27202

Drug	*Results*				*Total*
	Excellent	*Good*	*Fair*	*Poor*	
Group III, placebo	3	18	38	45	104
Group II, compound G27202	32	53	8	2	95
Group I, phenylbutazone	39	48	9	4	100

The perineal and abdominal wounds were inspected at regular intervals. There was no evidence of inflammatory reaction in the perineum, and the abdominal wounds were clean and showed no infiltration. Since all of the wounds were completely exposed and uncovered, there was easy access to the incisions. Antibiotic therapy was not used routinely. The blood pressure and pulse were checked daily and were found to be within normal limits. According to the standards of the American College of Surgeons there was no morbidity among the obstetric group, while only 3 of the gynecologic patients had some elevation of temperature which responded readily to antibiotics and of which the causative factor could not be determined. A white blood count and differential were taken on the fourth day. The count ranged from 8,000 to 12,000; there was no evidence of leukopenia or agranulocytosis. The differentials were within normal limits.

The side reactions accompanying the ingestion of this drug were minimal. Generally, the patients felt well and did not complain of dizziness, nausea, or vomiting.

Many of the obstetric patients stated that their postpartum course was much more comfortable than that which they had experienced in previous deliveries. There was no evidence of edema or salt retention and no demonstration of the stigmas of blood dyscrasia. Of the entire group, 3 patients developed skin eruptions; 2 had a moderately severe urticarial reaction and the other had a mild papular rash. One patient had slight nausea but not enough to necessitate the discontinuance of the drug (Table II).

Material

The uniform excellence of results in the pilot study provoked interest in additional evaluation of the anti-inflammatory drugs in the obstetric-gynecologic patients.

In 1955, Burns and associates[2] isolated a new agent from the urine of patients who had been treated with phenylbutazone. This is a parahydroxymetabolite which has the same beneficial effects as the parent drug, but in addition has the distinct advantage of being less toxic. This new compound is known as G27202. The preliminary reports from investiagtors[5, 6] indicate that this agent is as valuable as phenylbutazone by a ratio of 3 to 2, with perhaps a lessened incidence of side reactions (Fig. 1).

A further plan of investigation was advanced and carried out. This effort was limited to the obstetric patients while the gynecologic patients were still treated with the original preparation. The study consisted of 299 postpartum patients. They were divided into three groups of approximately 100 each. Group I had 100 patients who received phenylbutazone; Group II numbered 95; they received compound G27202; Group III were 104 in number; they received a placebo. These drugs were packaged individually and in no overt way appeared to be different from each other. The project was conducted in such a manner that neither the patient nor the administrator was aware of the category. The study has been completed, the code broken, and the results tabulated similarly to that in which the original group of patients were studied.

A review of the tabulated figures is striking. It became evident immediately that little relief from perineal pain was experienced in the group that received the placebo. This was reflected by the need of narcotics and additional therapy to make

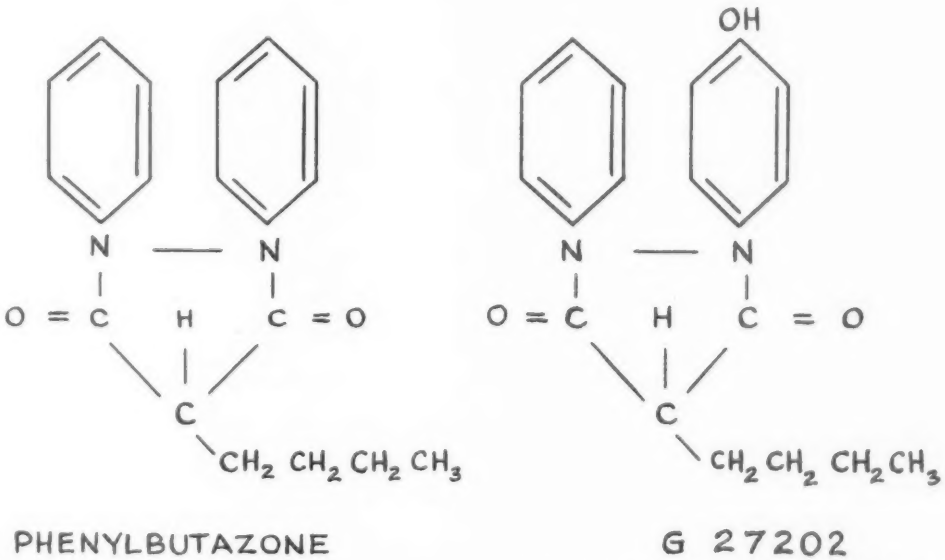


Fig. 1. Structural formula of phenylbutazone and the parahydroxy metabolite of phenylbutazone.

them comfortable. When questioned, 45 and 38, respectively, expressed fair and poor results from the treatment. Thus, 80 per cent obviously neded some other type of treatment for relief from the discomfort. When compound G27202 was used, 32 and 53, respectively, obtained excellent and good results; a percentage of 90 in favor of the drug. A similarly satisfactory response was revealed when 39 and 48 patients of the 100 treated with phenylbutazone showed excellent and good results (87 per cent).

The ones who received the placebo required supplementary narcotic preparations throughout their hospital stay, while in Group II (G27202) and Group I (phenylbutazone) narcotics were needed only within the first 24 hours, the maximum dose being three tablets of 32 mg. of codeine each. In an attempt to alleviate the pain during the first 24 hours, 400 mg. of the medication was given to each patient upon admittance to the hospital. If the labor progressed more than 12 hours, the dose was repeated. There were no conflicting effects with sedation used for alleviation of labor pain. Under this regime, 25 patients were treated with resultant diminution of narcotics to one or two doses of codeine.

In all of the patients studied, the side effects such as nausea and skin eruptions were so minimal that it was found unnecessary to record them. The white blood counts were within the range of 8,000 to 12,000 with no evidence of disturbance in relationship to leukopenia or agranulocytosis. This compared favorably with a control group of 30 who received no medication of this type and in whom the blood counts were within the same general range.

Comment

A perusal of the work of previous investigators reveals that there is a distinct advantage in the use of anti-inflammatory drugs in the treatment of patients with infectious and surgical diseases.[1, 3-6] From our studies, we are impressed with the fact that the use of phenylbutazone and the parahydroxy metabolite of the drug enhances the postpartum and postoperative comfort and healing process in the obstetric-gynecologic group. These drugs are contraindicated in patients with edema or cardiac and renal diseases, as well as in those who have a history of drug allergy or peptic ulcer, yet their value as an ancillary treatment in patients with surgical lesions, including the obstetric-gynecologic group, is encouraging.

It has been postulated that the local discomfort experienced by the postoperative and postpartum patient is due to the inflammatory reaction which results from the trauma of operation.[4] Therefore, it seems logical that any agent which could relieve or overcome edema, erythema, or cellular infiltration would be beneficial in relief of pain as well as expeditious in the process of healing.

Our experience has demonstrated that when these drugs are used narcotic preparations are not necessary after the first 24 hours. We hope that by giving the medication prior to delivery or operation the need for narcotic preparations will be further eliminated. With the discontinuance of other types of treatment such as wet or dry heat and analgesic sprays, there is also a lessened burden upon the nursing personnel, an incident of timely consideration.

We feel that more extensive exploration into the new metabolite and phenylbutazone in the treatment of inflammatory processes of the gynecologic patient is warranted. Several patients with inflammatory lesions of the pelvis were treated with this drug in conjunction with antibiotic therapy. The results were successful; there was speedier resolution of pelvic masses, relief of pain, and early return to normal physiologic function.

Summary and conclusion

1. The reaction to inflammation in infection and surgical diseases is questioned as a favorable phenomenon.

2. As in other surgical fields, the use of anti-inflammatory drugs in obstetric and gynecologic patients speeds recovery.

3. Compound G27202 and phenylbuta

zone have proved to be effective types of anti-inflammatory drugs.

4. In a pilot study 120 patients, obstetric and gynecologic, were given phenylbutazone. The results were excellent since pain relief was marked with the minimal use of narcotics and no other forms of treatment.

5. A double-blind study was carried out on 300 patients equally divided into groups receiving a placebo, compound G27202, a parahydroxymetabolite of phenylbutazone, and phenylbutazone.

6. The study substantiated the results found in the pilot study. In addition, compound G27202 was found to be as effective as the original compound.

7. When used over a short period of time phenylbutazone and compound G27202 are comparatively safe. There was no evidence of local infiltration in the surgical wounds and no edema or erythema. The patients' white counts and differentials were within normal limits and compared favorably with the counts of others who had not taken the drugs. There were practically no side reactions.

8. The use of anti-inflammatory drugs has proved to be a valuable contribution in the postoperative care of the obstetric and gynecologic patient.

We wish to acknowledge our gratitude to Dr. M. William Amster, Assistant Medical Director of the Geigy Pharmaceuticals, for the drugs used in this study and for his encouragement and cooperation. We also wish to express our thanks to Miss Mary Bostian, Mrs. Belle Caplan, Mrs. Jessie Garrison, and Mrs. Ruth Topper of the nursing staffs of the Sinai Hospital and The Hospital for the Women of Maryland, for their assistance.

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Puerperal hematomas

Analysis of 112 cases with a review of the literature

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RUEFF[47] reported the first case of puerperal hematoma of the birth canal in 1554. The sparsity of cases published since then[42, 63] would give the impression that this is one of the rarer complications of parturition. This seems to be confirmed by the low incidence reported by many observers.

It is our impression that this complication occurs with greater frequency than is generally realized. Therefore, it was decided to analyze the 112 cases of this entity that were observed at the Jewish Hospital of Brooklyn from January, 1933, to June 30, 1958. The purpose of this paper is: (1) to attempt to establish a realistic incidence of this complication, (2) to present the clinical aspects of this entity based upon our experiences and those in the literature, (3) to evaluate therapy and prognosis with current management, and (4) to emphasize that this complication is inherent in normal labor.

Incidence

The reported incidence of this entity varies greatly with different clinics. Michaels and Herring[33] reported an incidence of 1:3,344 deliveries; DeLee and Greenhill,[11] 1:4,000; Pimpaneau,[43] 1:2,500 to 3,000; Williams,[63] 1:2,000; Moschkow,[38] 1:1,951; and McElin, Bowers, and Paalman,[32] 1:561; the incidence at our institution was 1:937 deliveries. If hematomas of episiotomy wounds were included in our series and records were as accurate in the earlier as in the later years of this study, the true incidence would be about 1:300 to 1:500 deliveries. The great disparity in incidence can be attributed to the physician's failure to recognize the condition and inadequate records due to either a sense of personal embarrassment or an opinion that this is a complication of no significance. On the other hand, subperitoneal hematomas are truly a rarity as noted in our series and confirmed by a review of the world literature (Table I).

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Classification

Puerperal hematoma of the birth canal can be divided into four main groups, depending upon their location.

1. Vulvar type. The bleeding is limited to the vulvar tissue and is readily visible to the naked eye.

2. Vulvovaginal type. The hematoma involves the paravaginal tissue and the vulva, perineum, or ischiorectal fossa. The extent of the bleeding is only partially revealed on inspection of the vulva.

3. Vaginal or concealed type. The hematoma is confined to the paravaginal tissue and is not visible externally.

4. Supravaginal or subperitoneal type. The bleeding occurs above the pelvic fascia and is retroperitoneal or intraligamentous.

Another classification, which is nondescriptive, is based upon the time of occurrence. The hematomas are classified into two groups, an immediate and a delayed type. The delayed type results from pressure necrosis and occurs 24 or more hours post partum; DeLee[11] reported one occurring on the twenty-first day. The delayed type is rarely encountered and only one case in our series fell into this category; the hematoma developed on the third postpartum day.

Etiology

Many concepts have been advanced as to the cause of puerperal hematomas, but none of these are specific etiological factors. The marked vascularity and congestion of the pelvic tissues at the time of parturition appears to predispose to the formation of hematomas. In view of this it is remarkable that this complication is not a more common occurrence. It is our impression that the trauma inherent in normal labor is the specific etiological factor responsible for formation of hematomas and that this complication is a potential risk in every pregnant individual. This belief is substantiated by the fact that many cases have occurred prior to delivery, and the majority of the patients were delivered spontaneously. When the trauma of normal labor is enhanced by operative delivery, there is an increased incidence of hematomas. A review of the literature (Tables I and II) and the findings in this series (Table III) corroborate this. The greater force necessary to overcome the resistance of the nulliparous soft parts accounts for the majority of hematomas which occur in the primipara. Hematomas follow delivery of both term and premature infants.

In this series, the smallest infant weighed 1,800 grams and the largest more than 4,500 grams (Table IV). However, the incidence of infants of excessive size was twofold as great as that encountered in our clinic at large. Infant size, per se, may be a predisposing factor, and this impression is substantiated by the fact that 85 per cent of excessive-sized infants were delivered spontaneously. It would appear that any factor necessitating increased distensibility of the birth canal will predispose to rupture of a blood vessel without involvement of the overlying mucosa. The duration of labor was significant in only 2 cases in this series. In one, the trauma inherent in precipitous labor resulted in a hematoma despite the delivery of a premature infant, and in the other a prolonged second stage resulted in pressure necrosis with formation of hematoma on the third postpartum day. Thus, normal rather than abnormal labor was more frequently related to formation of hematomas. Varicosities have been implicated as a major factor predisposing to formation of hematomas. Braun-Fernwald[5] reported that varicosities of the vulva were an etiological factor in 80 to 85 per cent of the cases of vulvar hematoma. DeLee and Greenhill,[11] on the other hand, state that varices do not favor formation of hematomas. Marked vulvar varicosities were noted in 5 cases in this series and in each instance the hematomas formed prior to crowning. If varicosities were a significant etiological factor one could expect greater frequency of hematoma formation than is actually encountered and a greater incidence in parous rather than in nulliparous individuals. Leinzinger[27] noted that toxemia predisposed to the formation of hematomas. However, review of the literature and the findings in this study do not confirm this. Hematomas may also result from lack of hemostasis in the repair of an episiotomy. In these cases the bleeding is confined to the depths of the episiotomy incision with distention of the overlying suture lines, whereas in the type under discussion the hematoma cavity is usually away from the line of the episiotomy incision, and the episiotomy per se is generally not involved until late, if at all. In this connection it is interesting to note that the location of the hematoma corresponded to the side of the

Table I. Summary of 70 cases of subperitoneal hematomas reported in the literature

Author and year	No. cases	Parity			Mode of delivery			Location			Treatment			Pre-eclampsia	Deaths
		Primipara	Multipara	Not stated	Spontaneous	Operative	Not stated	Right	Left	Not stated	Conservative	Surgical	Not stated		
Williams[63] (review), 1904	34	16	9	9	25	6	3	15	8	11	23	2	9		18
Teller,[57] 1910	1		1		1					1		1			1
Elberfeld,[65] 1910	1		1		1					1		1			1
Hipsley,[20] 1925	1		1		1				1			1			1
Tenconi and Massari,[58] 1927	1	1			1				1			1			
Coulin,[9] 1929	1	1	1		1			1				1			
Moschkow,[38] 1932	3	2	1		2	1		2	1			3			1
van Vugt,[60] 1933	1			1		1				1		1			
Couvelaire and Lacomme,[8] 1933	1			1	1					1	1				1
Sontag Gandara and Schiavo,[54] 1939	2			2			2			2			2		
Vartamo,[61] 1940	4	2	2		3	1		2	2		2	2			
Michaels and Herring,[33] 1948	3	2	1			3				3	2	1		2	3
Walsh and Ganser,[62] 1948	1		1			1				1		1			
Kirchhoff,[24] 1948	1		1		1					1		1			
Shull and Thoms,[52] 1948	1		1		1				1			1			
Lyons,[31] 1949	1		1			1			1			1			
Beer and Kushner,[3] 1950	1		1			1		1			1				
McElin, Bowers, and Paalman,[32] 1954	7			7			7			7	6	1			
Riviere, Chastrusse, Boursier, and Biessy,[46] 1956	1	1			1				1		1			1	
Swaab,[56] 1957	1		1		1			1			1				
Ganser and Walsh,[15] 1957	1	1				1			1			1			
Sotto and Collins,[55] 1958	1			1			1			1			1		
Present series	1		1			1		1			1				
Total	70	26	24	21	40	17	13	23	17	30	38	20	12	3	26

episiotomy in 59 cases and was contralateral in 52 cases (Table V).

Blood dyscrasias and pudendal block are rare causes of hematomas and were not responsible for any cases in this series. Deep cervical lacerations, incomplete rupture of the uterus, and spontaneous rupture of a varicosity in the broad ligaments are responsible for the production of the subperitoneal type of hematoma.

Pathologic anatomy

The genitals at term are very vascular and contain abundant loose subcutaneous tissue into which bleeding occurs with little resistance. If the hemorrhage occurs beneath the levator ani muscles and pelvic fascia, the blood dissects downward along the fascial planes to cause swelling and discoloration of the labia on the same side. If the bleeding is severe enough it can continue its downward course into the ischiorectal space, the perineum, or the buttocks. If the resultant hematoma is large enough, it will displace the vagina and anus to the opposite side. Lipow[28] reports a case in which the hemorrhage was severe enough to cause complete disruption of the perineum. If the hemorrhage occurs above the pelvic diaphragm, a mass will protrude into the upper portion of the vaginal tube and the blood will dissect the peritoneum away from the adjacent structures and extend upward beneath the inguinal ligaments into the broad ligaments and parametrium. If the bleeding is sufficiently severe, the blood will continue its upward course retroperitoneally to involve the region of the kidney and eventually the lower margin of the diaphragm. Excellent anatomic illustrations can be found in R. J. Pieri's article.[42]

Symptomatology and findings

The symptomatology and findings are best discussed in relation to each variety of hematoma (Table VI). In the vulvar type, the most common complaint was severe perineal pain occurring either immediately or several hours after delivery. This was present in all cases of this variety. The pain is due not only to the tension developed by the extravasated blood, but also, in a large degree, to the disruption of the tissues. Vesicle tenesmus may be present. Occasionally, the tension of the extravasated blood causes pressure necrosis of the overlying skin with external bleeding and shock. This was present in only 2 cases of this variety. Examination readily reveals the extent of the tumefaction. The mass is cystic and tender. The overlying skin is edematous with bluish discoloration. Many cases remain undetected until late because the severe perineal pain is attributed by the attending physician to the episiotomy. Inspection will readily reveal or rule out a hematoma. In the partially concealed variety, as in the previous group, pain, perineal and pelvic, was the most common complaint, but vaginal bleeding was the most distressing symptom. The bleeding results through a rent in the overlying vaginal mucosa following pressure necrosis. The bleeding may occur either in the immediate postpartum period or many hours later, and is generally attributed to hemorrhage from an atonic uterus. Shock, with its attending train of symptoms, is quite common, and it occurred in 43 of the 56 cases of this type. Rectal and vesical tenesmus may be present. Early external examination may reveal nothing. Later, there is usually a brawny induration of the skin of the labia or perineum, followed by an ecchymotic discoloration. Sterile vaginal examination because of pain or bleeding readily discloses the extent of the tumefaction and any defect in the mucosa. In many cases the vaginal tube is almost completely obliterated by the tumor mass which pushes the overlying vaginal mucosa to the opposite side.

In the concealed variety, the symptoms are dependent upon the size of the hematoma. If relatively small, it is asymptomatic and usually goes undiscovered until a routine vaginal examination is performed. This was true in 6 cases of this type. If the hematoma is relatively large, pain, vaginal bleeding, and shock predominate. Vaginal bleeding may occur as late as 10 days post

Table II. Summary of 770 cases of vulvovaginal hematomas reported in the literature

Author and year	No. cases	Parity			Mode of delivery			Location
		Primipara	Multipara	Not stated	Spontaneous	Operative	Not stated	Right
Frank–Kamenetzky[14] (review), 1909	82	35*	34	13			82	40
Wimpfheimer[64] (review), 1910	117	49	32	36			117	
Reich,[45] 1910	1	1			1			1
Hirsch,[21] 1910	2	1	1		1	1		
Champeau,[6] 1914	17			17			17	15
Cherry,[7] 1917	1		1		1			
Petersen,[41] 1918	4	1	3		4			
Johannsen,[23] 1920	1	1			1			1
Danby,[10] 1924	2	2			2			1
Shaw,[51] 1924	1	1				1		
Krause,[25] 1925	1		1			1		1
Sahler,[48] 1925	31	21	10		25	6		18
Osler,[40] 1926	1		1		1			
Gibberd,[17] 1928	1	1			1			
Narvaez,[39] 1930	3	2	1		2	1		2
Morosoff,[36] 1930	1		1		1			1
Moschkow,[38] 1932	20	13	7		17	3		5
Argonz,[1] 1933	3	2	1		2	1		2
Benedetti,[4] 1938	3	2	1		3			2
Pio,[44] 1938	4	1	1	2	2		2	2
Horvath,[22] 1938	1		1		1			
Leinzinger,[27] 1939	9		1	8	1		8	
Digonnet,[12] 1939	13			13	13			
Sontag Gandara and Schiavo,[54] 1939	10	2		8	2		8	
Hamilton,[18] 1940	12	10	2		9	3		8
Vartamo,[61] 1940	21	17	4		19	2		14
Bottiroli,[66] 1940	3	3			2	1		2
Lipow,[28] 1941	1		1		1			1
Morgantini and Balaguer,[35] 1941	1	1				1		1
Lamm and Lamm,[26] 1942	1	1				1		1
Lubin and Horowitz,[30] 1944	4	1	3		3	1		3
Garcia Mayorca,[16] 1945	1	1				1		1
Duckman and Tortora,[13] 1947	1	1				1		1
Lubbers,[29] 1947	3	2	1		3			3
Walsh and Ganser,[62] 1948	2	2			2			1
Hannan,[19] 1948	1		1		1			
Kirchhoff,[24] 1948	4	3	1		4			2
Michaels and Herring,[33] 1948	14	8	6		8	6		9
Lyons,[31] 1949	2			2			2	
Saloheimo,[49] 1949	1		1			1		1
McNally and Ehrlich,[34] 1952	52	34	18		9	43		26
McElin, Bowers, and Paalman,[32] 1954	66			66			66	
Baldwin,[2] 1954	2	1	1		1	1		1
Samuelsson,[50] 1954	50	38	12		42	8		
Morrison,[37] 1956	1	1				1		

Location			Treatment					
Left	Bilateral	Not stated	Conservative	Surgical	Not stated	Toxemia (No.)	Deaths	Remarks
3	4	5	50	32			8	In 4 cases, hematoma formed following first twin; in 3 cases there were blood dyscrasias
		117			117			
			1					
2			2			2		
2					17			
		1	1					
		4	3	1				
				1				
1				2				
	1				1		1	Bilateral hematoma during labor; patient delivered by cesarean section
				1				
8		5			31			Cesarean section to deliver second twin following spontaneous delivery of first
1				1				
1				1				
1				3			1	
				1				
15			9	11				
1				3				
1			2	1				
		2		2	2			
		1	1					
1		8	8	1				
13					13		1	
2		8		2	8			
2		2	1	11		2	1	Sole death occurred in conservatively treated patient
6		1	17	4		4		
1			1	2				
				1				
				1				Hematoma incised to permit delivery of baby
			1					Hematoma developed on fourteenth postpartum day
1			1	3		1		
				1				
				1				
				3				
1				2		1		
1			1				1	
2			2	2				
4	1		1	13		6		
		2			2			
					1			Obstructed birth canal; cesarean section performed for delivery of twins
20		6	8	44		5		
		66	31	35		3		
		1	1	1		1		
		50	21	29				
1			-	1				

Table II—Cont'd

Author and year	No. cases	Parity			Mode of delivery			Right	Left
		Primipara	Multipara	Not stated	Spontaneous	Operative	Not stated		
Riviere, Chastrusse, Boursier, and Biessy,[46] 1956	1	1			1				1
Shulman, Ratzan, Grossbard, and Lawrence,[53] 1956	3	2	1		1	2			3
Trace,[59] 1957	24			24			24	6	18
Pieri,[42] 1958	95			95			95		
Sotto and Collins,[55] 1958	46	25	21		11	35		31	13
Authors' series	111	61	50		60	51		74	37
Total	770*	313*	186*	271*	258*	173*	339*	277†	193†

*Frank-Kamenetsky's cases not included in grand total.
†Wimpfheimer's cases not in grand total. Frank-Kamenetsky's data utilized instead.

partum and be confused with late postpartum hemorrhage due to retained placental tissue. If the tumor is large enough, it may obstruct the flow of lochia and cause lochia metria. Inspection of the perineum and vulva reveals no abnormality and only vaginal examination discloses the true diagnosis. In the subperitoneal variety, the predominant symptom is lower abdominal pain and/or loss of blood. However, it may be asymptomatic as was true in the only case in our series. The diagnosis is made upon finding a mass in the lower abdomen lateral to the uterus and confirming it by pelvic examination.

Puerperal hematomas may simulate hemorrhage from an atonic uterus, late postpartum hemorrhage, rupture or inversion of the uterus, neoplasms of the ischial spines, or vaginal cysts. A thorough abdominal and pelvic examination will readily differentiate these various possibilities.

Table III. Parity and mode of delivery in 112 cases of puerperal hematoma

Parity	
Primiparas	62
Multiparas	50
Mode of delivery	
Spontaneous	61
Low forceps	33
Midforceps	8
Breech	10

Management

The treatment is dependent upon the time of recognition of the hematoma. If it forms prior to delivery of the infant or the placenta, it is best treated expectantly unless the mass is progressing in size or is large enough to obstruct normal delivery. In the latter instances, the hematoma is incised, the clots evacuated, and the bleeding points ligated if possible. If the latter is not feasible, a temporary hemostatic pack is placed in the hematoma cavity. More definitive treatment should await completion of the third stage of labor. Occasionally, with an extensive hematoma, abdominal delivery may be necessary prior to evacuation of the tumefaction.

Table IV. Infant size in 112 cases of puerperal hematoma

Weight (grams)	No. cases
1,500-1,999	1
2,000-2,499	7
2,500-2,999	12
3,000-3,499	26
3,500-3,900	48
4,000-4,499	9
4,500-4,999	9

The vast majority of hematomas are recognized during the puerperium and definitive therapy can be readily accomplished

Location			Treatment			Toxemia (No.)	Deaths	Remarks
Left	Bilateral	Not stated	Conservative	Surgical	Not stated			
1			1					
3				3				
18				24				
		95			95			
13	2		14	32		3		
37			21	90		12	1	One patient had repeated hematomas in subsequent pregnancies
193†	8†	257†	199†	366†	170*	40	14†	

at this stage regardless of when the hematoma occurred. One has the choice of either watchful waiting or immedaite surgical intervention. With expectant management the mass is carefully observed and surgical intervention is carried out only if there are signs of active bleeding, as manifested by increasing size of the mass or progressive evidence of impending shock or if suppuration subsequently occurs. With expectancy, the hematoma is slowly resorbed or spontaneously evacuated. Occasionally it may become encysted and the wall calcified, requiring excision at a later date. This occurred in one of the patients who was treated expectantly, and the calcified mass was removed 3 months post partum.

In the past decade, almost all patients have been treated actively (Table VI). In recent years the tendency has been to perform primary repair whenever feasible rather than to pack the cavity prior to secondary repair. Surprisingly, many extensive disruptions can readily be repaired by primary suture after the bleeding points have been isolated and ligated. In these instances a tight vaginal pack is inserted prophylactically for additional hemostatic effect. If an attempt at primary repair reveals marked tissue friability, it is better to pack the hematoma cavity and vagina. If bleeding is in the rectovaginal septum, additional rectal tamponade may be readily and quickly accomplished through the insertion of an inflatable rectal bougie. This is far more effective rectal counterpressure than can be obtained from a rectal pack. If the rectal bougie is employed, it should be deflated every 8 to 12 hours and, after a 5 to 10 minute interval, reinflated. This will prevent possible necrosis of the rectal mucosa. The bougie or rectal packing is seldom required longer than 12 to 24 hours. The vaginal packing should be completely removed in 24 to 36 hours and a secondary repair then performed if there is no evidence of infection. The advantage of immediate secondary repair is that it decreases

Table V. Relationship of episiotomy to site of hematoma in 111 cases of vulvovaginal hematoma

Sit of episiotomy	
Right	84
Left	9
Median	16
No episiotomy	2
Location of hematoma	
Right	58
Left	53
Formation of hematoma	
Prior to delivery	10
After delivery	101
Hematoma site in relation to episiotomy	
Ipsolateral	59
Contralateral	52

Table VI. Symptoms and treatment in 112 cases of puerperal hematoma

Variety	No. cases	Symptoms					Transfusion		Treatment	
		Asymptomatic	Vaginal bleeding		Pain	Shock	Single	Multiple	Conservative	Surgical
			Early	Late						
Apparent	23	0	2	0	23	1	10	2	9	14
Partially concealed	56	0	45	0	56	43	21	28	4	52
Concealed	32	6	15	11	26	19	4	18	8	24
Subperitoneal	1	1	0	0	0	0	0	0	1	0

the convalescence period markedly. We have found little advantage in packing with absorbable hemostatic sponges, for this usually increases the morbidity, is not always readily absorbed, and interferes with secondary repair of the hematoma cavity. Blood replacement and adequate prophylactic antibiotics are essential components of the therapy.

In the subperitoneal or supravaginal variety, the treatment must be individualized according to the situation. If the mass does not increase in size, and the pulse remains good and the blood pressure is maintained, the patient may be treated expectantly. On the other hand, if evidence of continued active bleeding is found, immediate laparotomy should be performed, and a hysterectomy or ligation of the hypogastric artery may be necessary in order to secure hemostasis.

Prognosis

In the early part of the century, puerperal hematomas were associated with a high maternal mortality rate (Tables I and II). Today death from a hematoma is a rare occurrence. The only death in this series occurred in a patient with rheumatic heart disease who died in cardiac failure. The hematoma, in this instance, was a contributing rather than a causative factor of death. Similarly, infection of the hematoma is rarely encountered. The only complication of note has been a temporary renal shutdown in two instances. In both cases, the oliguria was secondary to extensive tissue destruction and hemorrhage. In each instance, renal output was normal within 48 hours.

Comment

The present series represents approximately one sixth of all the cases presented in the world literature and more than 50 per cent of the latter have been reported since 1954.[2, 55] It is evident, therefore, that the majority of cases have never been reported and that this entity is more common than is generally realized.

Although numerous factors predispose to formation of hematomas, the trauma inherent in normal labor is the only factor common to all the cases and is the specific etiological agent responsible for formation of hematomas. Thus, hematomas are generally unavoidable and are not a reflection on the obstetrician's capabilities.

Many of the hematomas discovered during the puerperium probably originated during the descent of the presenting part. The tamponade effect of the leading pole delayed the formation and recognition of the hematoma. Whether delayed hematomas are due to pressure necrosis or late recognition one cannot say with certainty. It is our feeling that the majority of these are due to a failure of early recognition.

Adoption of two measures will result in earlier recognition of hematomas: (1) routine inspection of the vulva and perineum immediately prior to sending the patient to the postpartum floor (this will usually enable one to detect hematomas in the vulvar and episiotomy sites) and (2) immediate vaginal examination of all patients com-

plaining of severe perineal pain in the early postpartum period. This will usually disclose not only the paravaginal hematomas, but also the vulvovaginal type before there is extensive disruption of the perineum and excessive loss of blood.

Summary

1. An analysis of 112 cases of puerperal hematomas of the birth canal are presented.

2. The physiological trauma inherent in normal labor is responsible for the rupture of the blood vessel that produces the hematoma.

3. Immediate operative intervention with primary repair is the treatment of choice whenever feasible. In the other cases, evacuation of the hematoma and packing of the cavity followed by secondary repair are indicated.

4. Delay in diagnosis is responsible for many of the more extensive perineal disruptions.

5. Hematomas occur more commonly than is generally realized.

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The electronic evaluation of fetal heart rate

IV. The effect of maternal exercise

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THE increased perinatal mortality associated with chronic hypertension and pre-eclampsia may be related to compromised uteroplacental function on the basis of diminished uterine blood flow.[1-7] Any mechanism which tends to interfere with uterine blood flow probably decreases oxygenation of the intervillous space and thereby lowers the total oxygen available for transfer across the placenta.

With the clearance time of injected radioactive sodium from the intervillous space and myometrium used as an index of uterine blood flow, Browne and Veall,[1] Moore and Myerscough,[6] and Morris and co-workers [4, 5, 7] were of the opinion that there was diminished uterine blood flow in hypertension,[1, 4, 6] pre-eclampsia,[1, 4, 6] the second stage of labor,[7] postmaturity,[6] and with maternal exercise.[5] Cox and Chalmers[2] and Johnson and Clayton[3] endeavored to measure uterine blood flow by determing the fetal uptake of Na^{24} intravenously injected into the mother and found that there was a delay in transfer to the fetus in toxemia of pregnancy.

During studies of electronically recorded fetal heart rate patterns of patient during labor with techniques previously described, [8-10] it was noted that with abnormal uterine activity, maternal hypotension, and in some cases of pre-eclampsia, definite types of bradycardia patterns were seen. These patterns were thought to be associated with fetal hypoxia due to diminished intervillous space blood flow.[10-12]

In view of the above studies which suggested that in certain situations, which included maternal exercise, there was decreased uterine blood flow, it was felt that maternal exercise may put a temporary additional load on uteroplacental reserve. Consequently, in situations where uteroplacental function may already be borderline and the margin of fetal reserve low, it may produce fetal heart rate patterns of the type thought to be due to fetal hypoxia,[10] and hence provide a means of evaluating fetal environment in conditions such as toxemia, hypertension, and postmaturity where relative fetal hypoxia may exist.[13, 14]

This report describes a limited study of the fetal heart rate patterns following ex-

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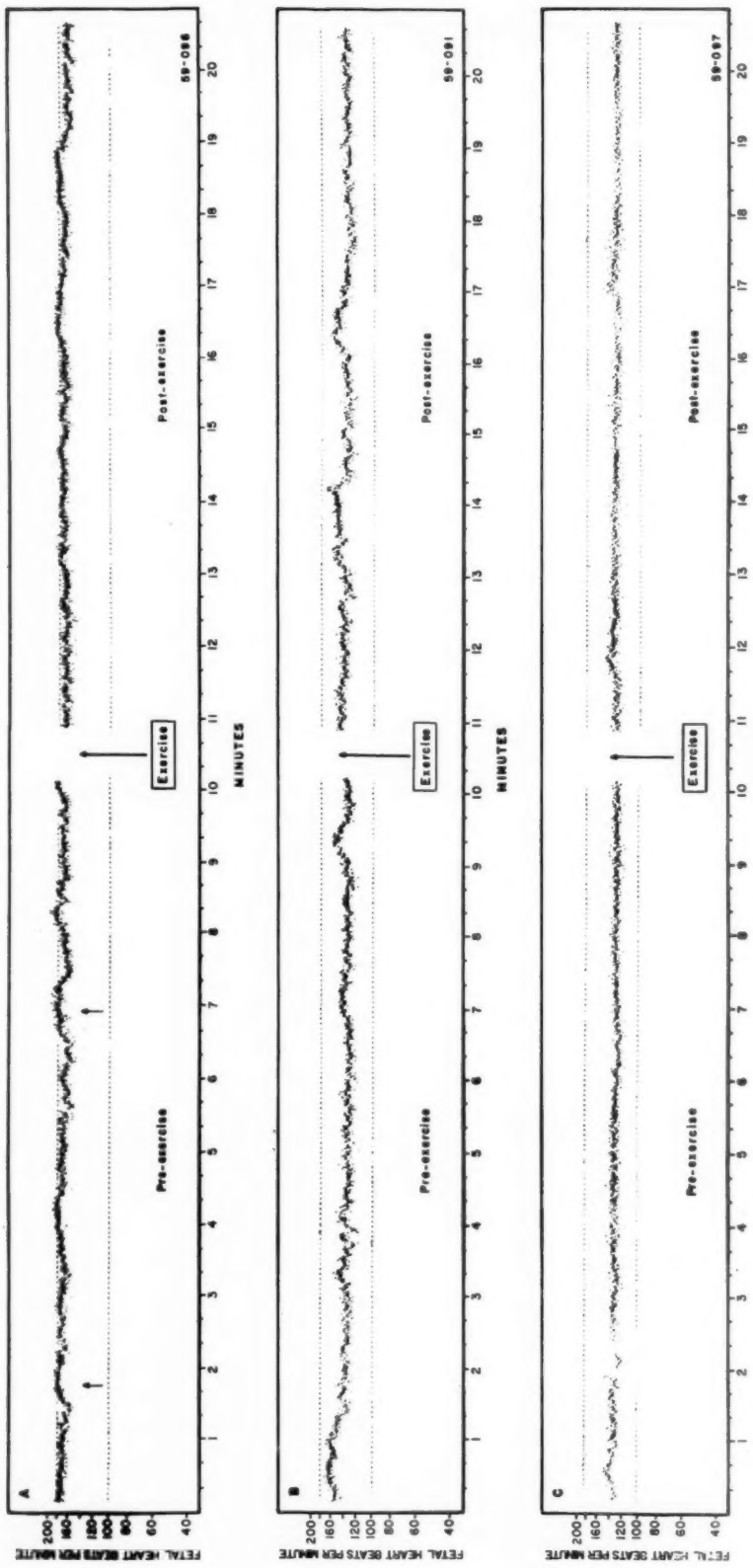


Fig. 1. *A-C,* Fetal heart rate patterns before and after maternal exercise observed in three 21-year-old primigravid patients. The pre- and postexercise patterns are not appreciably different. *A,* Normal antepartum course, 36 weeks of gestation. Arrows in pre-exercise baseline mark visible fetal movement. *B,* Normal antepartum course, 41 weeks of gestation. *C,* Mild pre-eclampsia, 40 weeks of gestation.

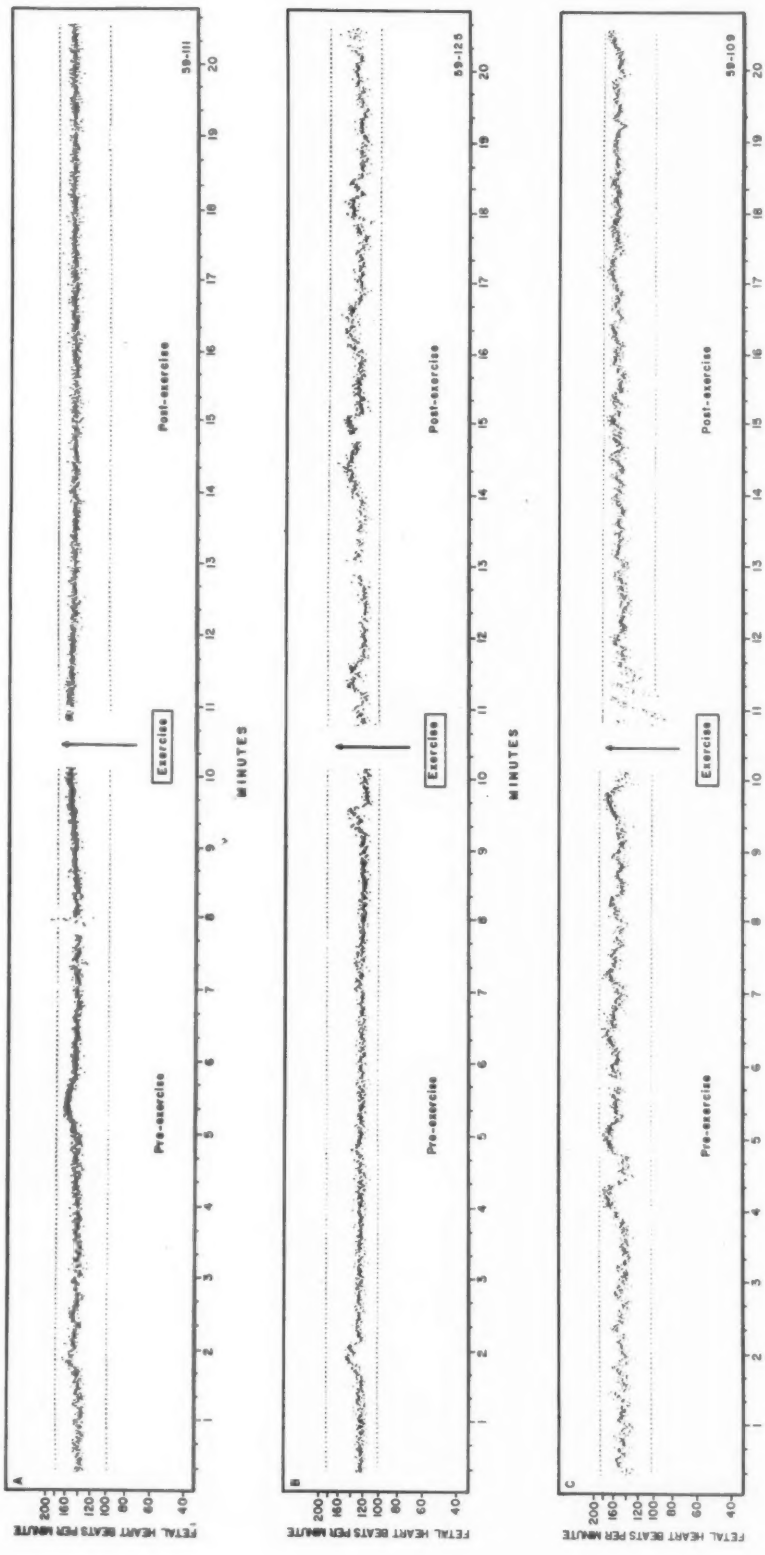


Fig. 2. *A-C*, Minor changes in the fetal heart rate following maternal exercise. *A*, A 33-year-old multipara, essential hypertension, 33 weeks of gestation. *B*, A 16-year-old obese primigravida, essential hypertension, 42 weeks of gestation. *C*, A 22-year-old primigravida, mild pre-eclampsia, 38 weeks of gestation.

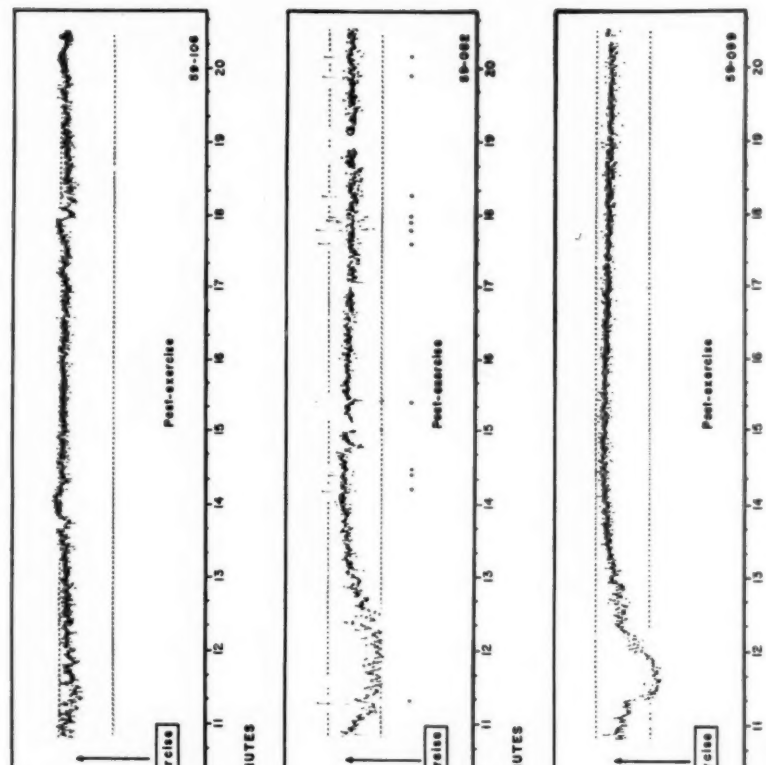


Fig. 3. *A*, Minor fetal tachycardia present in the postexercise tracing of a normal 25-year-old primigravida at 41 weeks of gestation. *B*, Transitory bradycardia following exercise of a normal 19-year-old primigravida at 39 weeks of gestation. Frequent premature ?nodal contractions are present in the original tracings but reproduced poorly in the above records. They are marked by "dots." *C*, Transitory fetal bradycardia and tachycardia following exercise of a mild pre-eclamptic 25-year-old obese primigravida at 40 weeks of gestation. Bradycardia begins almost immediately after exercise and is followed by tachycardia which persists for several minutes.

ercise of a group of patients with normal antepartum histories and a small number with chronic hypertension, pre-eclampsia, diabetes, and postmaturity. The care of the patients was not based on the patterns noted in the study but on the clinical judgment of the individual obstetrician in charge of each patient.

Patients and procedures

Forty exercise tests were performed by 26 patients from the Yale University and General Services of the Grace–New Haven Community Hospital. Nineteen patients had a gestation period of less than 42 weeks (10 had normal pregnancies, 5 had pre-eclampsia, 2 had chronic hypertension, and 2 had mild diabetes). Seven patients had a gestation period between 42 and 43 weeks, one of whom had essential hypertension (Fig. 2, *B*). Six patients were studied at weekly intervals during the last 6 weeks of gestation while the other 20 had one or two studies prior to delivery. In 8, the fetal heart rate was monitored continuously during labor.

Before the exercise test was begun, a 30 minute baseline tracing of the fetal heart rate was recorded with the patient supine in bed. The recording and data reduction methods have been described previously.[8, 9] The instantaneous fetal heart rate was plotted semilogarithmically.

Ten minutes of the record immediately preceding and following exercise have been used for illustration in Figs. 1-3, inclusive, and additional tracings in Figs. 4 and 5 where other material is shown.

The patient performed a standard amount of exercise based on age and weight in 3 minutes by climbing a 2 step platform. The platform and procedure used were similar to that described by Master and associates[15] for the evaluation of coronary insufficiency. The number of ascents was determined from a modification of tables[16, 17] constructed at Cornell University Medical College on the basis of blood pressure and pulse rates of healthy individuals returning to the resting level 2 minutes after the cessation of exercise. The amount of exercise which may be most useful for the primary purpose of this study has yet to be determined.

Immediately following exercise, the patient was returned to the pre-exercise supine position and continuous recording of the fetal electrocardiogram resumed. In all patients the fetal heart rate was followed for at least 30 minutes unless there was a marked deviation in rate, when it was followed until the rate returned to pre-exercise levels.

In the patients studied during labor, uterine contractions were determined by abdominal palpation and checked against increased baseline activity on the fetal ECG record.

While the observations were primarily concerned with the fetal heart rate response to maternal exercise, the fetal heart rate patterns during labor and the condition of the infant at birth (on the basis of the Apgar score[18]) were also recorded. The subsequent development of infants who had unusual fetal heart rate responses will be followed for the next few years.

Results

This series of 40 exercise studies is too small for adequate classification but in order to provide some measure of organization, three major categories were assigned on the basis of fetal heart rate changes following a "standard" exercise test: (1) no remarkable change, (2) minor change, (3) bradycardia, irregularity, and tachycardia.

On serial studies of the same patient the record from each visit did not always fall into the same category as on previous occasions. This was true only of categories 1 and 2. No real assessment can be made of the frequency of this change since the numbers involved are too small.

1. No remarkable change. Four of the 26 patients studied had tracings in which no remarkable fetal heart rate changes were observed in the postexercise period. Fig. 1, *A-C* illustrates the patterns observed in three 21-year-old primigravid patients. Fig. 1, *A* was recorded at 36 weeks of gestation from

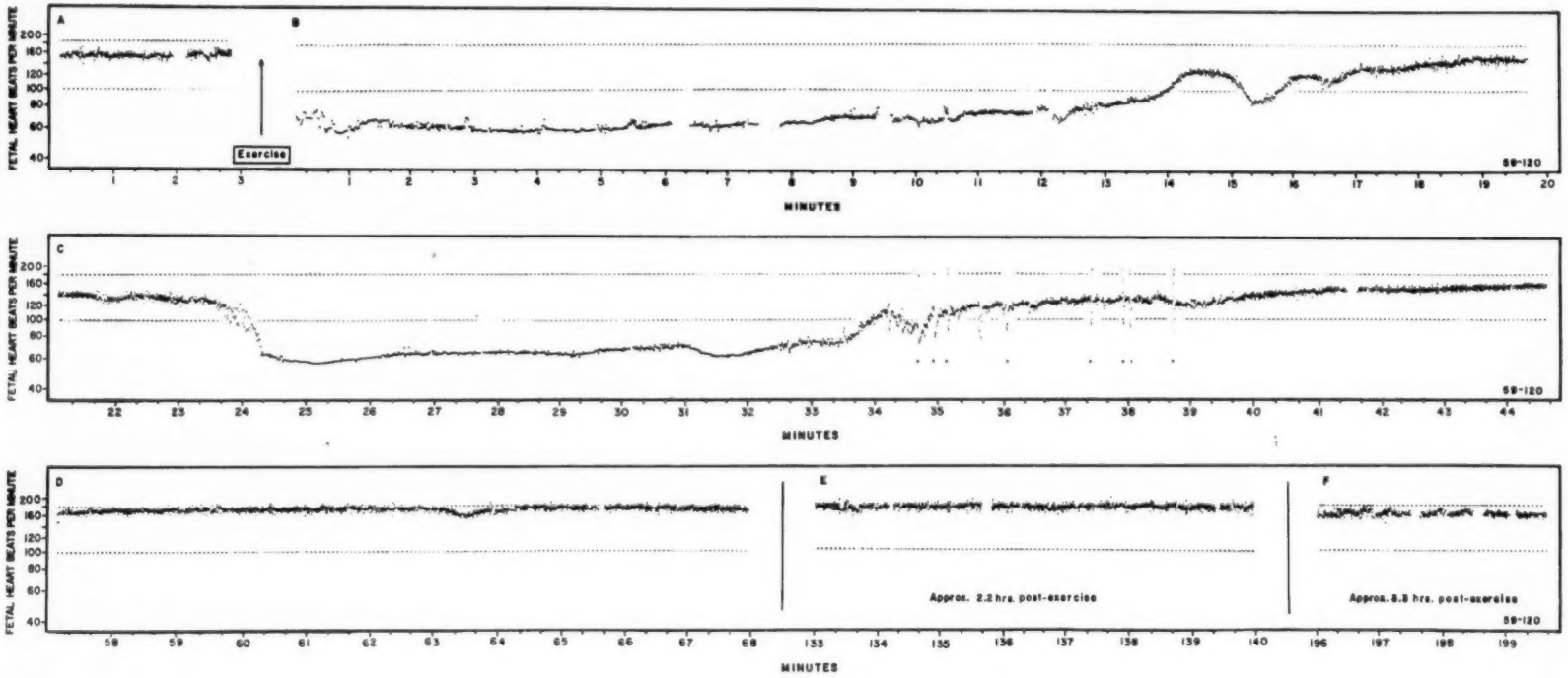


Fig. 4. Profound and prolonged fetal bradycardia followed by sustained tachycardia after exercise of a 27-year-old primigravida at 43 weeks of gestation. *A-F* are consecutive tracings of the same patient. *A*, A short segment of pre-exercise baseline. *B*, Profound fetal bradycardia of about 60 beats per minute which persisted for 14 minutes after exercise. *C*, Recurrence of fetal bradycardia (duration 11 minutes) 24 minutes after exercise. One hundred per cent oxygen was administered continuously beginning 30 minutes after exercise. Premature ?nodal contractions marked by "dots." *D*, Onset of fetal tachycardia of 170-180 beats per minute 58 minutes after maternal exercise. *E*, Persistent fetal tachycardia of 180 beats per minute 2 hours and 20 minutes after exercise. *F*, Return of the fetal heart rate to pre-exercise levels 3 hours and 16 minutes after exercise.

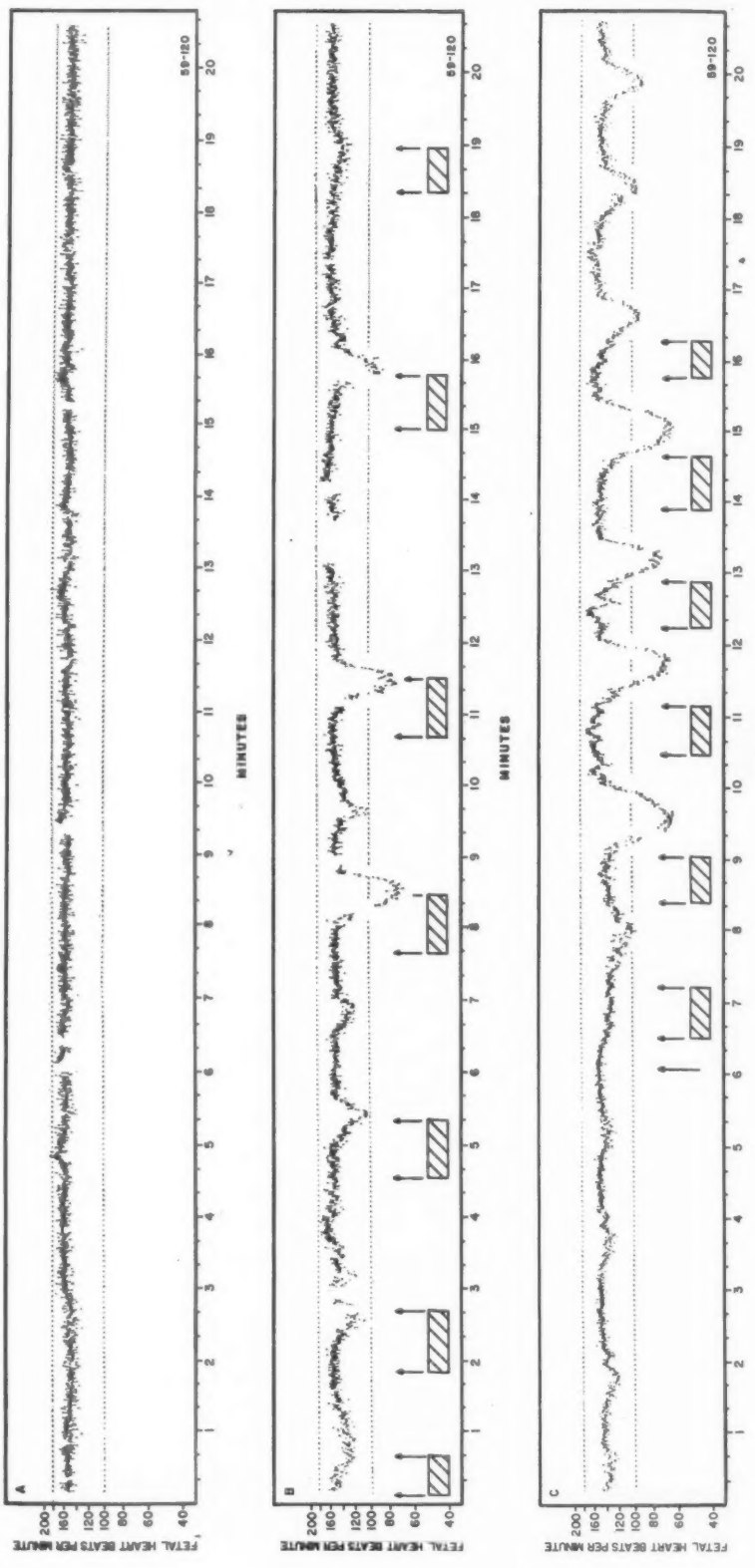


Fig. 5. *A-C,* Recordings made of fetal heart rate patterns of the same patient as Fig. 4, *A-F. A,* Normal fetal heart rate shortly before administration of oxytocin. *B,* Fetal bradycardia associated with mild, infrequent uterine contractions. Note the onset of bradycardia toward the end of the uterine contractions and its persistence into the interval between contractions. *C,* Profound fetal bradycardia associated with more frequent contractions. Arrow at left indicated an increase in the oxytocic infusion rate.

a patient with a normal antepartum course. A mild transient tachycardia noted in the pre-exercise baseline is marked by arrows and was coincident with visible fetal movement. The pre- and postexercise records are quite similar apart from these minor changes. Fig. 1, *B* shows a similar response with a normal patient at 41 weeks of gestation. The record of Fig. 1, *C* is also similar to that of Fig. 1, *A* and *B* and was recorded from a patient at 40 weeks of gestation who had been hospitalized for 4 days because of intermittent hypertension as high as 140/95. The subsequent antepartum course and delivery were uneventful. The infant at birth was in good condition.

2. Minor changes. Seventeen patients had patterns in this category. Figs. 2, *A-C* and 3, *A* have been selected to illustrate the magnitude of fetal heart rate variation noted with this group. The fetal heart rate pattern in Fig. 2, *A* was recorded at 33 weeks of gestation from a 33-year-old multipara who had essential hypertension (at the time of recording blood pressure was 170/110 mm. Hg). The minor fluctuation in the pre-exercise baseline disappeared after exercise. Fig. 2, *B* is the fetal heart rate pattern associated with exercise of a 16-year-old obese hypertensive primigravida at 42 weeks of gestation. A minor accentuation of a slight fetal heart rate irregularity can be seen after exercise. A 2,400 gram infant was delivered the next day. The placenta was small but not unusually infarcted or fibrotic.

Fig. 2, *C* is a tracing of a 22-year-old primigravida at 38 weeks of gestation with mild pre-eclampsia (blood pressure 140/80). There is mild fetal heart rate irregularity preceding exercise which is altered slightly after exercise.

The record of Fig. 3, *A* was made from a normal 25-year-old primigravida at 41 weeks of gestation. The very minor acceleration in fetal heart rate persisted for about 30 minutes.

3. Bradycardia, irregularity, and tachycardia. Six patients were in this category. Three had pre-exercise fetal heart rate irregularities which were accentuated by exercise (not illustrated). In 2 others fetal bradycardia was present for about one minute and then was followed by 5 minutes of tachycardia. The other patient's record after exercise showed profound fetal bradycardia which was followed by tachycardia of 170-180 beats per minute which lasted more than 2 hours.

Fig. 3, *B* illustrates transitory fetal bradycardia following exercise of a normal 19-year-old primigravida at 39 weeks of gestation. A fetal heart rate of 90 beats per minute had been detected in the antepartum clinic. Frequent premature ?nodal contractions were present in the pre-exercise and postexercise tracings (photographic reproductions poor). The infant was delivered 14 days later, weighed 3,055 grams, and was in good condition. The placenta was grossly normal.

Fig. 3, *C* shows transitory fetal bradycardia and tachycardia after exercise in a mild pre-eclamptic 25-year-old obese primigravida at 40 weeks of gestation. Bradycardia began almost immediately after exercise and was followed by tachycardia which persisted several minutes. After a trial of labor (no recordings made) a 3,975 gram infant was delivered by cesarean section for cephalopelvic disproportion. The baby was in good condition.

The tracing of Fig. 4, *A-F* is the most abnormal fetal heart rate pattern recorded by us in the past 4½ years. The patient was a 27-year-old primigravida at 43 weeks of gestation who had an uncomplicated antepartum course. Twenty-four hours before the tracing of Fig. 4, *A-F* her obstetrician heard a fetal heart rate of 70 beats per minute immediately after she had walked to his office. She was sent to the hospital for study and no fetal heart rate abnormalities were detected by auscultation. The fetal heart rate pattern (Fig. 4, *A*) after one hour of bed rest was normal. Because of the fetal bradycardia and postmaturity, Pitocin induction of labor was attempted; however the uterus contracted poorly and infrequently. Although the contractions were almost imperceptible by abdominal palpation

they were associated with fetal bradycardia (Fig. 5, *A-C*).

After the patient was rested overnight, an exercise test was performed. Fig. 4, *A* is a short segment of the pre-exercise baseline. Fig. 4, *B* illustrates the profound fetal bradycardia of about 60 beats per minute noted immediately after exercise which persisted for 14 minutes with subsequent gradual return to normal. With the patient still at bed rest another 11 minute episode of bradycardia occurred. This is shown in Fig. 4, *C*, which is a continuation, without interruption, of Fig. 4, *B*. One hundred per cent oxygen was administered continuously to the patient beginning 30 minutes after exercise. Thus, there is a total period of 25 minutes during which the fetal heart rate was less than 100 beats per minute. About 40 minutes after exercise the fetal heart rate gradually returned to pre-exercise levels. Frequent premature ?nodal contractions were noted while the rate gradually rose from 100 beats per minute (34 minutes after exercise) to 150 beats per minute (40 minutes after exercise). These are not seen well in the photographic reproduction of the record and have been marked by "dots."

Fig. 4, *D* is a continuation of Fig. 4, *C* and shows sustained fetal tachycardia of 170 to 180 beats per minute beginning 58 minutes after exercise. Fig. 4, *E* is the same tracing 2 hours and 20 minutes later. The tachycardia is still present. In Fig. 4, *F* a portion of the tracing taken 3 hours and 16 minutes after exercise shows the fetal heart rate back at pre-exercise levels.

Because of the fetal bradycardia associated with very mild uterine contractions and postmaturity, the private obstetrician decided to deliver the infant by cesarean section. This was done a few minutes after the recording of Fig. 4, *F*. At delivery the infant was covered with fresh meconium and the umbilical cord and membranes were stained green. The placenta was of normal size and was not unusually fibrotic or infarcted. There was no evidence of umbilical cord complications. The baby weighed 3,465 grams and was scored Apgar 9. The baby did well in the hospital and has continued to do so up to 4 months of age.

Fig. 5, *A* is a recording of the relatively stable fetal heart rate of about 150 beats per minute which was noted shortly after hospitalization. Fig. 5, *B* illustrates the "hypoxic" pattern of fetal bradycardia[10] associated with mild uterine contractions. The bradycardia starts toward the end of the contraction and persists into the interval between contractions. In Fig. 5, *C* profound fetal bradycardia is associated with more frequent contractions. The Pitocin infusion rate was increased at the arrow at the left of the tracing. The contractions as determined by abdominal palpation were mild and barely perceptible.

Comment

Twenty of the 26 patients of this limited study had no remarkable changes in fetal heart rate patterns following maternal exercise (Groups 1 and 2).

In the 3 cases of pre-exercise fetal heart rate irregularities which were accentuated by exercise, one fetus had the cord tightly wound around the neck three times, and one had a loop of umbilical cord prolapsed between the baby's head and the sacrum (cesarean section for postmaturity and cephalopelvic disproportion, baby weighed 4,680 grams); the umbilical cord of the third infant was flattened for about 4 inches where the umbilical vessels were markedly narrowed.

Three patients had bradycardia, irregularity, and tachycardia after maternal exercise. In 2 patients (Fig. 3, *B* and *C*) the changes were moderate but in the third, Figs. 4, *A-F* and 5, *A-C* the changes were marked. One patient (Fig. 3, *C*) was delivered by cesarean section for cephalopelvic disproportion; the other (Figs. 4, *A-F* and 5, *A-C*) was also delivered by cesarean section for "fetal distress" (fetal bradycardia associated with mild contractions).

This latter patient (Figs. 4, *A-F* and 5, *A-C*) during mild labor had a fetal heart rate pattern similar to that noted in certain pre-eclamptic patients in mild labor[12] and

whose fetuses did not tolerate labor so that a cesarean section was done because of "fetal distress." These patterns are similar also to those associated with strong and frequent contractions in normal patients.[10] The bradycardia occurs late in the contraction phase and persists in the interval between contractions and is usually followed by sustained tachycardia. In an earlier report[10] a hypothesis was advanced suggesting that this type of bradycardia was primarily hypoxic in nature and was related to interference with intervillous space blood flow. There is reason to believe that the intervillous blood flow is decreased with frequent and strong uterine contractions[19, 20] and in some cases of preeclampsia.[1, 4, 6] Very recent studies by Quilligan[21] indicate that at the acme of a strong uterine contraction there is a significant drop in intervillous space pO_2 which persists into the relaxation phase. It is possible that this patient may have had some compromise of uteroplacental function before exercise because:

1. The "hypoxic" fetal heart rate pattern associated with mild labor was similar to that noted with some pre-eclamptic patients whose fetuses had severe bradycardia in labor.[12]

2. If maternal exercise lowers uterine blood flow[5] it would add a further load to an already compromised uteroplacental function and produce an unusual fetal heart rate response to exercise.

3. The "hypoxic" type of fetal heart rate pattern following exercise is similar to that noted previously with uterine hypertonus[10, 12] and maternal hypotension.[11] Both conditions are thought to be associated with diminished intervillous space blood flow.[10, 19, 20]

4. The bradycardia is followed by sustained tachycardia which slowly returns to the pre-exercise level. This tachycardia may represent the recovery phase after hypoxia.

The evidence suggesting a low margin of fetal oxygen reserve in this instance, which was lowered further by maternal exercise and mild labor, is fragmentary but the findings are consistent with our present concept of intervillous space blood flow and its importance in fetal oxygenation. From the clinical standpoint, it is interesting to note that an infant was born in good condition after experiencing at least two episodes of bradycardia (of less than 100 beats per minute) totaling 25 minutes. Up to 4 months of age no developmental abnormalities have been found. The infant will be followed carefully for the next few years.

In a more representative study of the effect of exercise on fetal heart rate it is unlikely that such a high proportion of patients (6 out of 26) will show changes. Patients were selected who had pre-eclampsia, hypertension and diabetes, and who were at least 2 weeks post date.

A program to determine the possibility of using an exercise test for the evaluation of the margin of fetal oxygen reserve is planned. If the suggestions raised by this limited study are confirmed, such a test may be of value in determining the margin of fetal reserve in a given case and, hence, permit evaluation of uteroplacental function in the terms of an individual fetus. This would simplify immeasurably the handling of patients where diminishing fetal reserve is a hazard in continuing gestation.

Summary

1. Forty recordings (26 patients) of the fetal heart rate patterns preceding and following maternal exercise have been made.

2. Maternal exercise had little or no effect on the fetal heart rate patterns in 20 of the 26 patients studied. The changes in 5 of the remaining 6 patients were moderate, and they were marked in one.

3. Profound and prolonged bradycardia followed by sustained tachycardia was noted in one patient (primigravida, 43 weeks of gestation) after exercise. During mild labor the fetus had an "hypoxic" type of fetal heart rate pattern.

4. Maternal exercise may decrease uterine blood flow and, hence, put a temporary additional load on the uteroplacental oxygen transfer mechanism which under some circumstances may be reflected by an abnormal fetal heart rate pattern.

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Fetal blood studies

XV. The carbon dioxide concentration gradient between the fetal and maternal blood of humans

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THE observations to be presented here were made in an effort to gain a wider understanding of the circumstances that influence or modify the exchange of the respiratory gases between the fetal and the maternal blood in the placenta through a study of the exchange of carbon dioxide between fetus and mother across the three-layered placenta of the human. We sought to determine the concentrations of the physically dissolved carbon dioxide, of the plasma bicarbonate, and of hydrogen ions that exist in the fetal and maternal bloods in the steady state. Our hopes were not fully realized, for a steady state across the placenta is not easily maintained in circumstances that permit the fetal blood to be sampled; nevertheless, the data we have obtained do permit some inferences to be drawn about the steady state equilibrium.

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Material and methods

The 6 normal subjects upon whom observations were made were delivered on the Obstetrical Service at The Johns Hopkins Hospital. The method of delivery was by cesarean section, the indication for the operation being previous cesarean section. In each case the peritoneal cavity was entered under local infiltration with 1 per cent lidocaine. Two and a half per cent Pentothal sodium was administered intravenously immediately prior to the uterine incision.

The technique employed for obtaining blood samples from the intervillous space and umbilical vessels was the same as that previously described.[1]

Bloods were transferred to a centrifuge tube under oil, and cells and plasma separated by centrifugation at 3,000 rpm. The carbon dioxide content of each plasma sample drawn from the centrifuge tube and transferred to the Van Slyke pipette by means of an oiled syringe was determined by the manometric method of Van Slyke and Neill[2] on 0.5 ml. samples.

The pH of each sample was determined by means of a Beckman pH meter, Model G, which had been previously standardized with a buffer of known pH. The results thus ob-

tained were corrected to 38° C. by means of Rosenthal's equation for plasma.[3]

$$\text{Plasma pH } 38° = pH_T - 0.0118\ (38\text{-}T) \quad (1)$$

where T is the temperature at which the pH of the plasma was measured.

Knowing the total carbon dioxide content and pH of each plasma sample, the physically dissolved carbon dioxide was calculated from the Henderson-Hasselbalch equation.

$$pH = 6.10 + \log \frac{\text{Total } CO_2 - \text{Dissolved } CO_2}{\text{Dissolved } CO_2} \quad (2)$$

The carbon dioxide tension in millimeters of mercury was then calculated from the dissolved carbon dioxide by means of the Bunsen coefficient.

$$pCO_2 = \frac{\text{Dissolved } CO_2}{0.0301} \quad (3)$$

where 0.0301 is the quantity of carbon dioxide in millimols, dissolved in one liter of plasma at standard temperature and pressure per mm. Hg of carbon dioxide tension, and where the concentration of dissolved carbon dioxide is also expressed in millimols per liter.

Results

The measured and calculated values obtained by the methods described are shown in Table I. As may be seen, the table is divided into a first group of 4 cases and a second series of 2. The first group comprised those in whom fetal samples were obtained within one minute of the sampling of the intervillous space. The second group of values represent 2 patients in whom difficulty was encountered in the delivery of the infant's head so that an interval of 4 to 5 minutes elapsed between the sampling of the intervillous space and the umbilical vessels.

From the data in Group I it may be seen that despite variations in the maternal plasma bicarbonate concentration and hydrogen ion concentration, the carbon dioxide tension was on an average about 7.0 mm. higher in the fetal than in the maternal vessel. The fetal carbon dioxide pressure was always the higher, the difference between it and the maternal carbon dioxide tension being from 3.2 to 7.0 mm. Hg at the arterialized end (umbilical vein minus intervillous space) and from 4.9 to 11.2 mm. Hg at the venous end (umbilical artery minus intervillous space).

The 2 patients in Group II, in whom sampling of the cord vessels was delayed, are of special interest. As can be seen from the table the carbon dioxide pressure gradients in these cases were 17.5 and 20.5 mm. Hg, respectively, or about three times the normal value. At the arterialized end the pressure differences were 14.5 and 20.5 mm. Hg, respectively, and at the venous end, 20.6 mm. Hg in the first case.

We have expressed the carbon dioxide gradient across the placenta in terms of pressures and have assumed that pressure differences can be spoken of when gas transfer occurs between two liquid phases. One should realize, however, that concentration difference constitutes more accurate terminology under these physical circumstances.

Comment

A review of the literature reveals that there are no previous data on this particular aspect of placental transfer in the human. Other studies have been concerned with the carbon dioxide relationship between the maternal peripheral vessels and the umbilical circulation at the time of delivery. By virtue of the fact that the exchange of carbon dioxide between fetus and mother occurs across the placenta such data are therefore not strictly analogous to ours. If it be remembered, however, that blood in the intervillous space is a mixture of arterial and venous blood, some useful comparisons can be made with the data in the literature.

Of major interest is the difference in relationship between the hydrogen ion concentrations in the fetal and maternal circulation seen in the two groups of subjects. The pH differences between maternal and fetal blood reported in our second group (delayed sampling) are of the same order of magnitude

Table I. Data obtained on blood samples drawn from placental vessels—carbon dioxide pressure gradient and difference in physically dissolved carbon dioxide across the human placenta

Duration of pregnancy (weeks)	*Vessel*	*Plasma CO_2 (mM./L.)*	*pH 38° C.*	*Plasma bicarbonate (mM./L.)*	*P_{CO_2} (mm. Hg)*	*FP_{CO_2}-MP_{CO_2}* (mm. Hg)*	*Physically dissolved CO_2 (mM./L.)*	*Differences in physically dissolved CO_2*	
								Umbilical vein minus intervillous space	*Umbilical artery minus intervillous space*
Group I									
39	Intervillous space	23.1	7.33	21.70	42.1		1.28		
	Umbilical vein	24.4	7.29	22.90	49.1	8.4	1.48	0.20	
	Umbilical artery	25.1	7.27	23.50	52.8		1.59		0.31
39	Intervillous space	20.1	7.41	19.07	31.0		0.93		
	Umbilical vein	24.0	7.41	22.79	37.0	8.2	1.11	0.18	
	Umbilical artery	27.4	7.42	26.04	41.4		1.25		0.32
37	Intervillous space	22.0	7.36	20.80	37.9		1.13		
	Umbilical vein	23.9	7.36	22.55	41.1	7.2	1.24	0.11	
	Umbilical artery	27.3	7.34	25.67	49.1		1.48		0.35
38	Intervillous space	21.6	7.36	20.40	37.2		1.12		
	Umbilical vein	23.5	7.35	22.10	41.3	4.5	1.24	0.12	
	Umbilical artery	25.0	7.37	23.60	42.1		1.27		0.15
Group II									
38	Intervillous space	20.3	7.40	19.24	32.1		0.97		
	Umbilical vein	25.3	7.33	23.77	46.5	17.5	1.40	0.43	
	Umbilical artery	26.3	7.29	24.56	52.7		1.59		0.62
39	Intervillous space	18.9	7.44	18.03	27.4		0.82		
	Umbilical vein	26.3	7.33	24.53	47.9	20.5	1.44	0.62	
	Umbilical artery	—	—				—		—

*FP_{CO_2} = fetal carbon dioxide pressure; MP_{CO_2} = maternal carbon dioxide pressure.

as those reported by others.[4, 5, 6] The cases in our first series, however, are strikingly different—the hydrogen ion concentrations on the two sides of the placental barrier are virtually identical. Accordingly, these data do not agree with the concept that there is a considerable pH gradient maintained across the placenta and within the fetus.

Since the preparation of this report we have had several occasions to confirm the finding that the more a steady state is approached, the more closely identical the maternal and fetal hydrogen ion concentrations will be. Furthermore, if it be remembered that it is at any given time technically easier to obtain a low fetal blood pH than a high one, we should add that the possibility exists that the carbon dioxide gradient described in our first group may well represent a higher figure than that which exists in utero. Actually, it may be more accurate to state that in our cases the mean carbon dioxide pressure gradient averaged not more than 7.0 mm. Hg, remembering that the existence of a smaller carbon dioxide gradient in utero may well have been present without our having been able to achieve sampling conditions compatible with the determination of such a gradient.

That not even all the samples obtained in our first group of cases were ideal may perhaps be inferred from the fact that the carbon dioxide tension in the intervillous space ranged from 27.4 to 42.1 mm. Hg and the pH from 7.33 to 7.44, whereas numerous studies have shown that the pH of blood in the pregnant woman is not different from that in the nonpregnant[7-13] while the pCO_2 of arterial blood in pregnancy is of the order of 32 mm. Hg.[7, 12-16] It is therefore of inter-

est that carbon dioxide gradients of the order described in Group I were found to occur with intervillous space carbon dioxide pressures ranging from 31.0 to 42.1 mm. Hg, which would tend to suggest that the size of the carbon dioxide gradient is not dependent on the absolute value of the carbon dioxide pressure in the maternal circulation, but rather on the carbon dioxide pressure in the fetal circulation.

The close relationship between the pH of the blood found on either side of the placental barrier has further importance from the point of view of oxygen transfer across the placenta. It has recently been suggested by Beer and associates[4] that since a relatively large pH gradient is maintained across the placenta (data supported by those of Kaiser and co-workers[5] and James and associates[6]), the Bohr effect would tend to superimpose the fetal oxygen dissociation curve upon that of the mother in vivo. While this circumstance in itself would not abolish the oxygen pressure gradient across the placenta, it would certainly not facilitate it. Our data from the subjects in Group I are not in agreement with this concept and suggest that the maternal and fetal oxygen dissociation curves in vivo are not normally superimposed. Furthermore, the concept of Beer and his colleagues regarding superimposition of the maternal and fetal oxygen dissociation curves in vivo is based on the assumption that the Bohr effect on maternal and fetal blood is identical. This is certainly not the case for the goat,[17] sheep,[18] and llama,[19] and we have had occasion recently to confirm this finding in the human.[20]

Finally, from the comparative physiologic point of view, our data are of interest. Studies of the carbon dioxide gradient have now been made in the cow,[21] sheep,[22, 23] goat,[22, 24] rabbit,[25] and man. In man, sheep, goat, and cow there appears to be a difference in carbon dioxide pressure of 6 to 10 mm. Hg between the two bloods, the fetal of course being the higher. In the rabbit the difference is so small that a definite gradient could not be established.

Summary

The concentrations of physically dissolved carbon dioxide, of bicarbonate, and of hydrogen ions in the plasma drawn from the principal vessels serving the human placenta —intervillous space, umbilical vein, umbilical artery—have been determined at the end of pregnancy and at the time of cesarean section.

The data indicate that the difference in concentration of dissolved carbon dioxide between the two sides of the placental barrier is about 0.22 mM. per liter, the fetal being the higher. In every case the bicarbonate concentration was greater in the fetal than in the maternal plasma. The pH of fetal blood was either the same or minimally lower than that of maternal blood.

Some of the implications of the data have been discussed.

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Nomograms and empirical equations relating oxygen tension, percentage saturation, and pH in maternal and fetal blood

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IN THE recent surge of interest in the measurement of the various parameters affecting oxygenation of the human fetus, frequent use has been made of oxygen dissociation curves to estimate the oxygen tensions existing in maternal and fetal blood when the percentage saturation with oxygen of their hemoglobin has been measured.

In the past, three main methods of constructing such oxygen dissociation curves have been used: (1) at constant pCO_2, usually 40 mm. of mercury, (2) at pH 7.40 or pH 7.40 ± 0.02, (3) at *any* pH with subsequent recalculation or "correction" of the points thus obtained to a given, desired pH.

The first method described above has the drawback of producing oxygen dissociation curves which vary in their position with the concentration of bicarbonates existing in the sample of blood with which the oxygen dissociation curve has been constructed.

The second method has the drawback of providing oxygen dissociation curves which can be used only to relate oxygen tension to the percentage saturation of the hemoglobin if the pH of the blood is 7.40 or 7.40 ± 0.02.

The third method has been used with the assumption that: (a) the correction factor used, calculated by Dill and associates[3] and derived by studies carried out with the blood of adult males, is equally applicable to that of pregnant females and (b) that such a correction factor, if it were to be the same for the adult male and the pregnant female, is also applicable to the fetus.

In order to confirm or disprove the latter premise and to obviate some of the drawbacks involved in the first two methods described above, we have sought to reinvestigate this entire question. The results of this investigation form the substance of this report.

On the basis of the results obtained, two empirical equations, one for maternal blood and one for fetal blood, are given, enabling one to calculate the third variable when the two other variables involved in determining the position of the oxygen dissociation curve are known.

Using these two empirical equations, we have provided two nomograms relating the three variables (pO_2, pH, and percentage saturation) in maternal and fetal blood, respectively, thus obviating the need for calculation of the desired variable when the other two are known.

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**Senior Research Scholar, Joseph P. Kennedy, Jr., Memorial Foundation.*

***Student Research Fellow, Josiah Macy, Jr., Foundation, 1959-1960; Henry Strong Denison Scholar, 1960-1961.*

Materials and methods

For these studies, the blood of 12 pregnant women and 12 newborn infants was used. Maternal blood was obtained from the antecubital vein by venipuncture and fetal blood from the umbilical vein immediately after delivery. Then 27 ml. of blood was drawn into syringes containing 3 ml. of an oxalate-fluoride mixture containing 2 per cent $K_2C_2O_4$ and 0.6 per cent NH_4F. The blood samples were equilibrated in 250 ml. tonometers containing various mixtures of oxygen and carbon dioxide.

On the basis of data previously reported in the literature, such oxygen tensions were used as were likely to produce percentages oxygen saturation of the hemoglobin varying between 20 and 80 per cent.

The carbon dioxide tensions used were chosen to provide wide variations in the ultimate pH of the blood samples and ranged for the maternal blood from 10 to 80 mm. Hg and for the fetal blood from 0 to 100 mm. Hg. Equilibration of the blood and gas samples was performed in a rotating water bath at 38° C. for a period of 15 minutes, after which the pressure in the tonometers was brought to atmospheric levels by permitting the excess of gas mixture in the tonometers to bubble out just below the surface of the water in the bath. The barometric pressure was read at this time and corrected to dry gas pressure by subtraction of the water vapor pressure. After a further 15 minutes of equilibration, the blood samples were drawn anaerobically into oiled syringes, capped, and stored in ice until analyzed.

Blood was analyzed for oxygen concentration by the method of Van Slyke and Neill.[18] The percentage saturation of each sample was calculated by dividing the oxygen concentration in each sample by the oxygen concentration in a sample of blood equilibrated in a tonometer with room air at 38° C. The concentration of oxygen physically dissolved in the plasma was subtracted from the total oxygen concentration in each sample prior to this calculation. The final composition of the gas mixtures in each

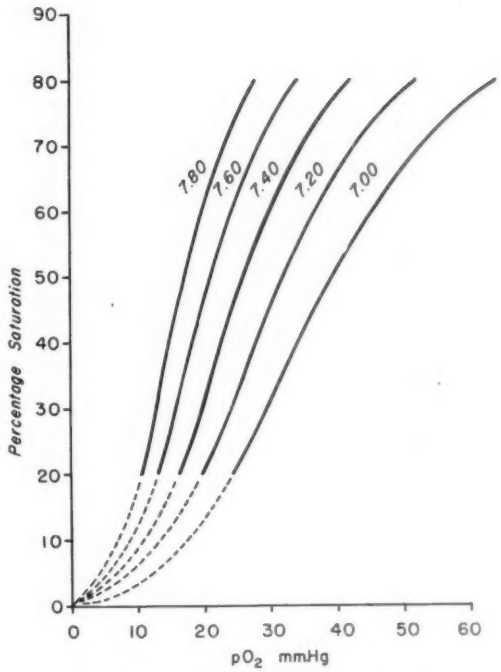


Fig. 1. O_2 dissociation curves of maternal human blood prepared at pH's 7.00 to 7.80.

tonometer was analyzed by the method of Scholander.[16] The pH of each blood sample was determined by means of the Beckman Model G pH meter.

The values of the pH thus obtained were corrected to a temperature of 38.0° C. by means of the Rosenthal factor.[15]

Results

In Table I we have reported the values obtained for pH, corrected to 38° C., percentage saturation with oxygen of the hemoglobin and the pO_2 with which the blood was equilibrated in the tonometers. The fourth column, both for maternal and fetal blood, gives the value for pO_2, which the empirical equation relating the three variables would give, while the last column gives the difference between the observed and calculated values for pO_2. In the case of the oxygen dissociation curves for fetal blood, we have also given the gestational age as calculated from the first day of the last menstrual period.

It will be seen that the fetuses ranged in

age from 268 days to 287 days. The position of the oxygen dissociation curves between these gestational ages is found to be unchanged. This is in keeping with findings previously reported in the literature.[12]

When the statistical method of least squares was applied to the data in Table I, empirical equations were derived giving the relationship between the three variables for maternal and fetal blood, respectively.

For maternal blood the following equation was obtained:

$$\log pO_2 = \underset{(\pm\ 0.015)}{4.734} - \underset{(\pm\ 0.011)}{0.448}\ pH + 0.351 \log \frac{S}{100 - S}$$

(coefficient of variation 0.012)

For fetal blood the equation we obtained was:

$$\log pO_2 = \underset{(\pm 0.012)}{5.748} - \underset{(\pm\ 0.011)}{0.601}\ pH + 0.389 \log \frac{S}{100 - S}$$

(coefficient of variation 0.014)

With use of these empirical equations, Figs. 1 and 2 were produced showing the position of the oxygen dissociation curves for maternal and fetal blood, respectively, at pH 7.0, 7.2, 7.4, 7.6, and 7.8.

With the same empirical equations, the nomograms in Figs. 3 and 4 for maternal and fetal blood, respectively, were constructed, thus obviating the need for calculation of the third variable, when the other two variables are known.

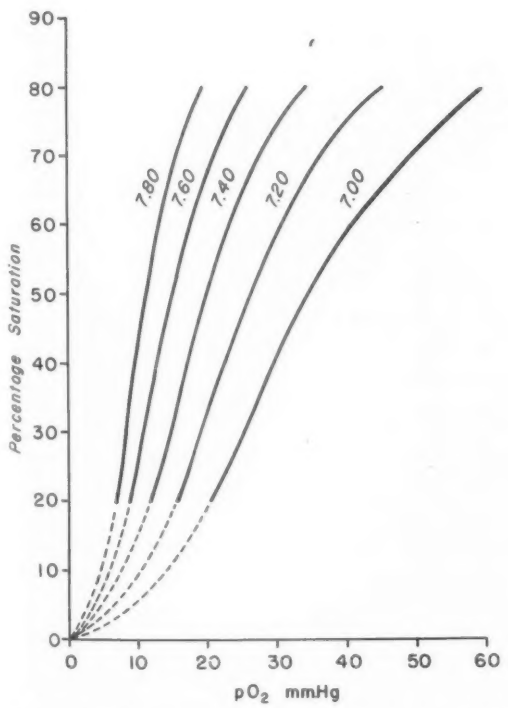


Fig. 2. O_2 dissociation curves of fetal human blood prepared at pH's 7.00 to 7.80.

Comment

It has been previously demonstrated[6] that the oxygen dissociation curves of maternal and fetal blood can be described between saturation levels of 20 to 80 per cent by the following equation:

$$\log pO_2 = K_1 - K_2\ pH + K_3 \log \frac{S}{100 - S}$$

where K_1, K_2, and K_3 are constants.

If the pH is held constant, the above equation is a rearrangement of Hill's equation[7] and the constant n of Hill's equation can be represented in terms of our data by the equation:

$$n = \frac{1}{K_3}$$

The applicability of this equation to oxygen dissociation curves between 20 and 80 per cent saturation of the hemoglobin with oxygen is again suggested by the close approximation of the calculated and observed values for pO_2. Similarly, the treatment of the fetal and maternal data as individual homogeneous groups also receives further support from this approximation.

While the fact that the applicability of this equation relates only to saturation levels between 20 and 80 per cent makes the equation's usefulness limited in pulmonary physiology, the same cannot be said for its usefulness in the study of the exchange of oxygen across the human placenta, since the percentage saturation of hemoglobin with oxygen in the intervillous space and in the umbilical vessels rarely exceeds 80 per cent. The error involved in applying this equation to saturations above 80 per cent has been well documented in the literature.[6]

Table I

Maternal blood					*Fetal blood*					
		pO_2						pO_2		
pH 38° C.	*Percentage saturation*	*Observed mm. Hg*	*Calculated mm. Hg*	*Δ pO_2 mm. Hg*	*Gestational age (days)*	*pH 38° C.*	*Percentage saturation*	*Observed mm. Hg*	*Calculated mm. Hg*	*Δ pO_2 mm. Hg*
7.699	65.8	25.54	24.10	−1.44	273	7.778	29.5	8.70	8.40	−0.30
7.694	34.1	15.36	15.27	−0.09		7.772	42.6	10.64	10.58	−0.06
7.689	49.3	19.99	19.15	−0.84		7.767	57.7	13.58	13.51	−0.07
7.679	61.2	22.94	22.94	0.00		7.739	69.8	16.55	17.24	+0.69
7.588	32.8	17.33	16.68	−0.65						
7.587	26.2	14.82	14.93	+0.11	276	7.703	23.3	8.33	8.22	−0.11
7.581	52.0	23.01	22.25	−0.76		7.688	31.9	10.31	9.94	−0.37
7.581	40.2	20.02	18.80	−1.22		7.669	45.5	12.21	12.78	+0.57
7.563	48.7	22.88	21.62	−1.26		7.654	56.4	15.32	15.48	+0.16
7.557	41.6	20.03	19.67	−0.36						
7.557	35.1	17.89	17.86	−0.03	280	7.637	37.2	11.05	11.68	+0.63
7.554	28.7	15.18	16.16	+0.98		7.632	48.7	13.34	14.14	+0.80
7.482	28.5	16.19	17.34	+1.15		7.614	56.4	16.33	16.35	+0.02
7.475	33.2	18.89	18.87	−0.02		7.604	66.8	18.33	19.69	+1.36
7.472	29.4	17.18	17.79	+0.61						
7.470	35.3	19.96	19.60	−0.36	270	7.472	24.0	10.92	11.50	+0.58
7.454	65.4	30.31	30.80	+0.49		7.467	31.9	13.60	13.49	−0.11
7.454	37.6	20.82	20.63	−0.19		7.462	45.1	17.38	16.90	−0.48
7.451	57.0	27.17	27.30	+0.13		7.456	54.3	19.21	19.68	+0.47
7.451	49.7	24.09	24.63	+0.54						
7.451	37.9	20.36	20.79	+0.43	280	7.377	38.4	17.37	17.08	−0.29
7.450	34.4	19.67	19.72	+0.05		7.375	54.2	22.71	21.98	−0.73
7.440	46.8	23.81	23.92	+0.11		7.370	46.0	19.44	19.43	−0.01
7.435	63.7	29.70	30.64	+0.94		7.370	60.8	25.56	24.61	−0.95
7.430	57.3	27.56	28.03	+0.47						
7.430	42.8	22.67	22.82	+0.15	268	7.305	49.3	24.45	22.44	−2.01
7.419	72.7	32.80	36.07	+3.27		7.305	44.6	21.90	20.85	−1.05
7.324	61.5	34.41	33.25	−1.16		7.292	63.4	30.54	28.61	−1.93
7.319	30.3	20.18	21.16	+0.98		7.292	58.4	27.14	26.37	−0.77
7.314	55.3	29.81	30.70	+0.89	273	7.292	35.1	17.62	18.18	+0.56
7.314	37.4	23.93	23.78	−0.15		7.292	26.0	14.57	15.36	+0.79
7.309	27.9	20.13	20.51	+0.38		7.277	48.6	23.49	23.07	−0.42
7.304	48.0	28.51	27.98	−0.53						
7.304	41.0	24.50	25.33	+0.83	272	7.267	30.0	17.91	17.18	−0.73
7.299	62.2	33.16	34.47	+1.31		7.261	23.1	15.69	15.09	−0.60
7.159	63.4	40.90	40.55	−0.35		7.259	36.2	20.33	19.40	−0.93
7.154	56.1	38.32	36.62	−2.30		7.254	45.4	23.90	22.66	−1.24
7.133	60.6	38.42	39.95	+1.53						
7.126	67.4	42.56	44.66	+2.10	280	7.260	28.7	16.99	16.94	−0.05
7.122	54.4	35.89	36.97	+1.08		7.250	45.5	24.52	22.82	−1.70
7.074	55.5	42.52	39.45	−3.07		7.250	43.4	21.89	22.07	+0.18
7.074	49.8	38.79	36.39	−2.40						
7.074	41.7	34.07	32.44	−1.63	285	7.102	36.4	23.52	24.18	+0.66
7.074	35.9	30.76	29.77	−0.99		7.098	53.2	31.00	31.77	+0.77
						7.097	27.7	19.89	20.82	+0.93
						7.093	42.7	27.08	27.13	+0.05
					287	7.094	29.0	20.93	21.43	+0.50
						7.089	34.7	23.94	23.91	−0.03
						7.085	41.2	27.08	26.79	−0.29
						7.069	47.1	29.29	30.06	+0.77
					271	7.024	57.0	36.16	37.32	+1.16
						7.019	59.8	39.32	39.35	+0.03
						7.019	48.6	31.76	32.98	+1.22
						7.019	40.2	26.96	28.87	+1.91

It should be clear that the error involved in applying the equation to values of less than 20 per cent saturation is bound to be less since all dissociation curves below those saturation levels tend toward zero.

With respect to the constant K_2, representative of the "pH effect" on the position of the oxygen dissociation curves, our data show that this constant is statistically significantly different for maternal and fetal blood (0.45 and 0.60, respectively). A similar difference has been found to be applicable to the oxygen dissociation curves for blood of maternal and fetal goats[6] (K_2 = 0.527 and 0.623, respectively) and llamas[10] (K_2 = 0.443 and 0.307, respectively). In sheep, the K_2 of 6 pregnant animals' blood varied from 0.325 to 0.479 and that of 3 fetal blood samples from 0.404 to 0.540. The number of sheep studied was insufficient to determine whether K_2 was statistically significantly different for maternal and fetal blood.[9]

The K_2 for maternal blood in our data (0.45) is not statistically significantly different from that reported by Dill and associates[3] for blood of adult males.

It should be stressed that since K_2, like the other constants in this equation, is derived empirically from a set of experimental data, this does not mean that the constant K_2 represents the magnitude of the *cause* of the shift in the position of the oxygen dissociation curves. The equations given in this report describe a mathematical association between positions of oxygen dissociation curves and pH, as measured on whole blood. Thus, no cause-and-effect relationship between the plasma pH given and the positions of the oxygen dissociation curves should be read into these data, and it is well to remember that K_2 is not representative of intracellular pH. For this reason, as has been previously pointed out,[9] at least part of the difference in oxygen affinity between maternal and fetal blood when compared at equal plasma pH could be due to a different intracellular-extracellular hydrogen ion concentration ratio.

With respect to K_3, which is the reciprocal

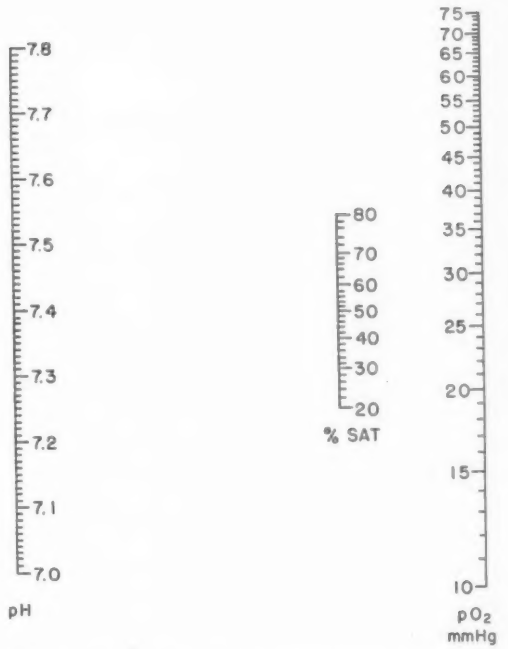


Fig. 3. Nomogram for O_2 dissociation curve, maternal blood.

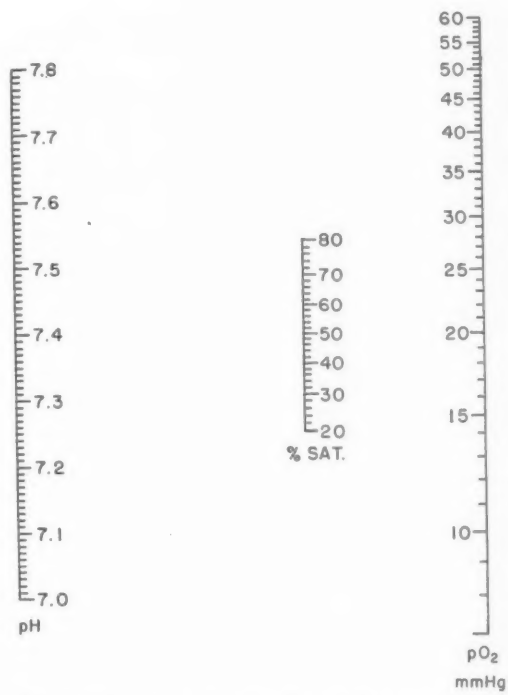


Fig. 4. Nomogram for O_2 dissociation curve, fetal blood.

of Hill's constant n, our data show no statistically significant difference between the maternal and fetal bloods. The same absence of statistically significant differences between the K_3 for adult and fetal bloods was previously reported for the goat[6] (n for maternal blood = 2.79, n for fetal blood = 2.66), and for the llama[10] (n for maternal blood = 2.43, n for fetal blood = 2.37). The previously cited sheep data[9] showed an n for maternal blood of 2.67 to 2.84 and an n for fetal blood of 2.35 to 2.76, the data again being insufficient for analysis regarding statistical significance. This constancy of n in the same species during development is again confirmatory of Riggs' data on the hemoglobin of the bullfrog[13] in which, despite a pronounced difference in oxygen affinity, n has the same value for tadpole and adult bullfrog hemoglobin. Our data, therefore, offer further confirmation of a previously published statement[9] that, in general, during development only certain properties of the hemoglobin molecule change while others remain constant.

By means of the nomograms shown in Figs. 3 and 4, comparison of most published oxygen dissociation curves becomes simpler than was heretofore possible. Thus, a comparison of the pO_2 required to half saturate the hemoglobin of adults' blood reveals the following:

At pH 7.40 Dill and co-workers obtained 50 per cent saturation at pO_2 26.3,[3] Beer and associates at 26.5,[1] Darling and coauthors at 27.6[2] and Prystowsky and associates at 26.0,[11] while our present data put the pO_2 required at 26.24 mm. Hg.

Beer and co-workers obtained their figures by using Dill's correction factor ($\Delta \log pO_2 = -0.48\ \Delta pH$), and we have seen that this correction factor is not statistically significantly different from ours for maternal blood. Comparison of our data with the oxygen dissociation curves of Eastman and collaborators[4] and Leibson and others,[8] who constructed their dissociation curves at constant pCO_2, is also possible. Thus, Eastman and associates obtained 50 per cent saturation of the hemoglobin with oxygen at a pO_2 of 32.0 mm. and Leibson and coauthors at 31.0 mm. Hg. From the nomogram in Fig. 3, it can be inferred that the blood pH at which these dissociation curves were constructed must have been 7.21 and 7.24, respectively. Knowing the pH and pCO_2 at which these oxygen dissociation curves were constructed, it is therefore possible, by using the Henderson-Hasselbalch equation, to say that the bicarbonate content of the blood used in the construction of their dissociation curves must have been 15.48 and 16.56 mM. per liter, respectively. Since their blood samples were obtained at vaginal delivery, it is interesting to note that such bicarbonate concentrations in maternal blood at the time of delivery correspond well with those in unpublished data of our own.[17] Thus, it may be seen that differences between oxygen dissociation curves for maternal blood heretofore published are explainable on the basis of physiological circumstances involved in their obtention. The minor differences existing between the dissociation curves published at pH 7.40 are well within the experimental errors for the various biochemical determinations involved and can further be partially explained by the fact that some dissociation curves were constructed at a temperature of 38° C., others at 37° C., some at pH 7.40, others again at 7.40 ± 0.02, while application of Dill's K_2 of 0.48 rather than a K_2 of 0.45 as derived from our data (though not statistically significantly different) would further contribute to the minor differences in the results reported.

The oxygen dissociation curves for maternal blood reported by Haselhorst and Stromberger[5] give the pO_2 required to half saturate hemoglobin with oxygen as 45, 31, 29, and 37 mm. Hg for the 4 patients reported on. From the nomogram in Fig. 3, it may therefore be concluded that these dissociation curves were constructed at pH 6.9, 7.24, 7.30, and 7.07, respectively. These presumably would have been the blood pH's. According to the aforementioned authors, the pH representing these values would have been 7.29, 7.36, 7.35, and 7.31, respectively

Their curves, therefore, lie considerably to the right of ours at the same pH.

With use of the nomogram in Fig. 4, a similar comparison also becomes possible for published fetal oxygen dissociation curves. Thus, the pO_2 required to half saturate the hemoglobin of fetal blood with oxygen was reported by Beer and associates as being 22.0, by Darling and co-authors as being 21.9, by Rooth and others[14] as being 21.0, and by Prystowsky and co-workers as being 19.0 mm. Hg. Of these figures, it may be said that Beer's and Rooth's are based on correcting experimentally obtained values to a pH of 7.40 by use of Dill's correction factor ($\Delta \log pO_2 = -0.48\ \Delta pH$). We have already seen, however, that the K_2 for fetal blood is statistically significantly different from that for maternal blood and should be 0.60. Thus, no strict comparison can be made between the data of the above authors and those here reported.

The pO_2 required to half saturate the hemoglobin with oxygen reported by Darling and associates is 21.9 mm. Hg at 37.0° C., while the previous data issued from this laboratory were published at a pH of 7.40 ± 0.02 and, therefore, agree within the limits of experimental error with the data in the present report. The pO_2 yielding half saturation of the hemoglobin with oxygen at pCO_2 40 mm. reported by Eastman and Leibson and their collaborators were 24.5 and 24.0 mm. Hg, respectively. Reference to the nomogram in Fig. 4 tells us that the pH of these blood samples at pCO_2 40 must have been 7.26 and 7.27, respectively. The bicarbonate concentration in these blood samples must, therefore, have been 17.32 and 17.76 mM. per liter at the time of vaginal delivery, and these figures are again within the ranges found by us under such circumstances.[17]

The pO_2 required to produce half saturation of the hemoglobin with oxygen in fetal blood reported by Haselhorst and Stromberger was 35, 25, 27, and 30 mm. Hg for the 4 cases reported upon. From the nomogram in Fig. 4, it will therefore be seen that the blood pH of the samples must have been 7.01, 7.25, 7.19, and 7.12, respectively. The pH reported on for these figures were 7.31, 7.34, 7.24, and 7.26, respectively. Again, therefore, their dissociation curves lie appreciably to the right of ours for identical pH.

It is hoped that the availability of the nomograms in this report will make the study of fetal-maternal gas exchange in terms of oxygen tensions rather than percentage saturations of the hemoglobin: (a) easier in the absence of oxygen electrodes and (b) more meaningful in relation to the acid-base balance between mother and fetus even with the availability of oxygen electrodes.

Summary and conclusions

1. Oxygen dissociation curves for blood of mothers and fetuses have been constructed at various pH's.

2. Any point on the maternal oxygen dissociation curve between 20 and 80 per cent saturation of the blood with oxygen can be calculated from this equation:

$$\log pO_2 = 4.734 - 0.45\ pH + 0.351 \log \frac{S}{100 - S}$$

3. Any similar point on the fetal oxygen dissociation curve can be calculated from the equation:

$$\log pO_2 = 5.748 - 0.60\ pH + 0.389 \log \frac{S}{100 - S}$$

4. Based on these equations, nomograms have been constructed and are included in this report.

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Oxygen saturation in the newborn infant

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OXYGEN saturation studies in the newborn were undertaken in 1930, when Eastman[5] first investigated this aspect of neonatal life. These studies required the use of large amounts of cord blood. Further work was not carried out until accurate determinations could be made with use of smaller blood samples. In 1942, Smith and Kaplan[17] used cord blood in an attempt to determine the time necessary for the attainment of normal neonatal oxygen saturation levels. At about this time, Millikan[12] described an oximeter which could be used to determine oxygen saturation in the peripheral blood. In 1949, Wood and his associates[3, 26, 28] modified this instrument so that exact and direct readings could be obtained.

This instrument, with slight modifications, has since been used widely. Between 1951 and 1955, Taylor and his co-workers,[18-20] using both capillary blood studies and oximetry, made significant contributions to the field. Since there were now two methods of determining oxygen saturation, several men compared the relative merits of these methods for investigative purposes. In 1950, Wood[28] showed that the standard deviation of the difference between simultaneous Van Slyke and single scale ear oximeter determination was approximately 4 per cent in hypoxic patients, with an average saturation level of 85 per cent. In 1957, Howard, Bruns, and Lighty,[8] using a single scale ear oximeter, compared determinations of arterial oxygen saturation with gasometric determination (Roughton and Scholander method) and found a difference of 5 per cent in levels below 80 per cent saturation and even closer correlation at the higher oxygen saturation levels. In 1957, Broch and Haarsted,[1] in a comparative study of the ear oximeter and chemical analyses, concluded that the two methods were in agreement. They found that the ear oximeter was more practical and more accurate than the chemical analysis method.

In 1957, Shields and Taylor,[16] using this instrument, demonstrated that in complicated obstetric cases where there was heavy sedation, the oxygen saturation in the newborn infant was considerably slower in achieving normal levels. Watts[23] and Walker[21, 22] also found a diminution in the oxygen saturation levels in complicated obstetric cases. Watts[23] also noted that deep ether anesthesia contributed further to this diminution. MacKay,[9] using cord blood, demonstrated that nitrous oxide anesthesia may cause a dangerous lowering of oxygen saturation.

In the recent literature there has been some doubt cast, not on the measurement of oxygen saturation and its accuracy, but on the interpretation of its meaning. Pennoyer and her associates[2, 6, 14] published extensively on oxygen saturation studies in the newborn

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and neonatal periods. Although she was able to demonstrate that a relationship did exist between cord oxygen levels and clinically observed anoxia, there was no relationship between cord oxygen at birth and the performance of behavior tests made on the infants between 24 and 48 hours of age. She concluded that the measure of oxygen saturation, while having a high face validity and objectivity, does not provide a satisfactory measure of what is clinically regarded as anoxia. Cross[4] also felt that the neonatal circulatory status may be a more important clinical condition than oxygen saturation in determining the condition of the newborn infant and the eventual prognosis.

Westin[24, 25] investigated the oxygenation in the fetus by means of hysterophotography. He accomplished this in the 14 to 18 week pregnancy group and found that the fetus appears much pinker than fetuses of comparable size at delivery. He also felt that the cyanosis of the fetus after delivery in therapeutic abortions suggests that the oxygen content of the cord vessels is lower after delivery than in intrauterine life. Pennoyer and associates[14] further showed that fundal pressure during delivery depressed oxygen saturation in the infant. McClure[11] in a recent publication demonstrated the efficacy of oxygen administration during the second stage of labor, but found certain shortcomings in the use of the oximeter.

This investigation was undertaken to study the oxygen saturation of the blood of the newborn infant and to evaluate the effect on oxygen saturation of certain drugs used as analgesic and anesthetic agents in labor and delivery. The peripheral oxygen saturation, as determined by ear oximetry, was used as an indication of drug effect on the mother and the newborn infant.

A single scale absolute reading alternating current ear oximeter was used with an infant sized earpiece for newborn babies and an adult sized earpiece for the mothers. One hundred thirty-four cases were studied. These were made up of both ward and private patients at full term, without selection, on the Maternity Service at Michael Reese Hospital. These cases were supervised by different members of the staff, and many different types, combinations, and quantities of analgesic drugs and anesthesia are reflected in the series. As soon as possible after birth the earpiece was attached and readings were taken every 2 to 5 minutes for approximately 30 minutes after delivery. The various categories were then studied and compared.

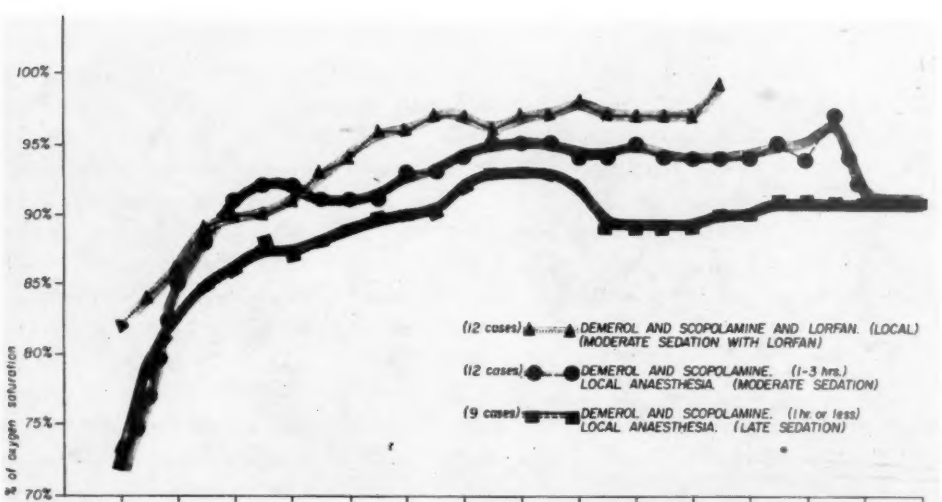


Fig. 1. The effects of Lorfan in the local anesthesia group on the moderately sedated patient.

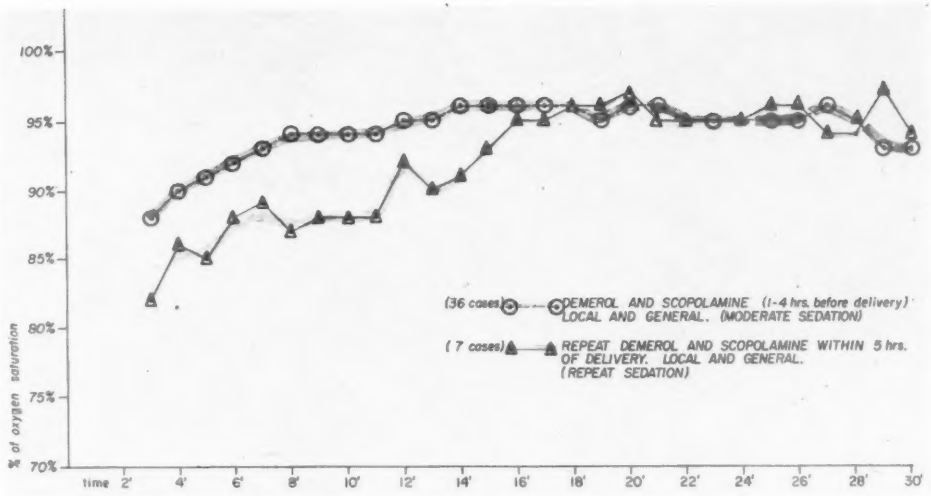


Fig. 2. The effects of repeat sedation within five hours of delivery.

Results

The cases studied fall into the following categories:

Group I. No analgesia or anesthesia. 18 cases.

Group II. Moderate sedation in labor. 36 cases. Essentially, this group received meperidine hydrochloride,* 100 mg., and scopolamine, 0.4 mg., from 1 to 4 hours prior to delivery.

Group III. Late sedation. 16 cases. Comparable to Group II, but sedation administered within 1 hour of delivery.

Group IV. Repeat sedation. 7 cases. Sedation was administered twice within 5 hours of delivery, the repeat dose being either Demerol or scopolamine, or both.

Group V. Levallorphan tartrate† plus moderate sedation. 23 cases. Either 1.0 mg. of Lorfan was co-administered with each 100 mg. of Demerol or the Lorfan was administered from 10 minutes to one hour prior to delivery.

Group VI. Promazine hydrochloride‡ plus minimal sedation. 15 cases. Sparine, 25 mg., was co-administered with Demerol, 50 mg., and scopolamine, 0.5 mg.

*Demerol, Winthrop Laboratories, New York, New York.

†Lorfan, Hoffmann-La Roche-Inc., Nutley, New Jersey.

‡Sparine, Wyeth Laboratories, Philadelphia, Pennsylvania.

Group VII. Major obstetric complications with varying amounts of sedative drugs. 10 cases. Typical of this group are prolonged labor, intrapartum infection, fetal embarrassment, and prolonged second stage of labor.

Group VIII. Breech presentation with varying amounts of sedative drug. 9 cases.

In the above groups the additional factor of type of delivery anesthesia is important. Deliveries were accomplished under local, pudenal block, or ethylene and oxygen general anesthesia. The simple perusal of the per cent figures of the oxygen saturation in the above broad groups is relatively unrevealing and does not permit statistical analysis. When the accumulated data are compared so that the only significant variable is the drug or anesthetic technique under consideration, the effect of these agents becomes apparent.

The following comparisons reveal certain observations of significance.

Fig. 1 compares moderate sedation early in labor, moderate sedation late in labor, and moderate sedation with co-administered Lorfan. In all of these cases delivery was under pudendal block anesthesia. The graph reveals a lower level in the oxygen saturation of the infant when sedation was administered late in labor. In the Lorfan group, within 10 minutes after birth, moderately higher

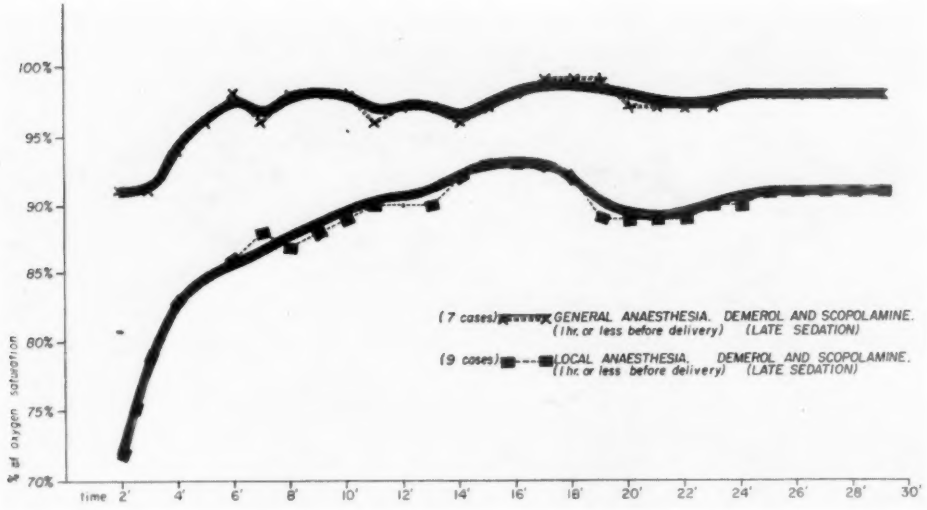


Fig. 3. The effects of general anesthesia when sedation is used late in labor.

oxygen saturation of the infant was present.

Fig. 2 compares moderate and repeat sedation. Both local and general anesthesia were used in this group.

Repeat sedation caused a lag in oxygen saturation of the infant which persisted to 16 minutes after birth. Thereafter, the oxygen saturation in the two groups was comparable.

Fig. 3 compares the use of pudendal block with general anesthesia (ethylene-oxygen) in the late sedation group. Those babies delivered under pudendal block in this group had a persistent decrease in oxygen saturation after birth for the 30 minutes under observation.

Fig. 4 compares moderate, late, and minimal with Sparine groups. These patients were delivered under general (ethylene-oxygen) anesthesia. In the group receiving Sparine, the oxygen saturation of the infants was lower for 14 minutes after delivery.

Fig. 5 compares breech and moderate sedation groups. Both local and general an-

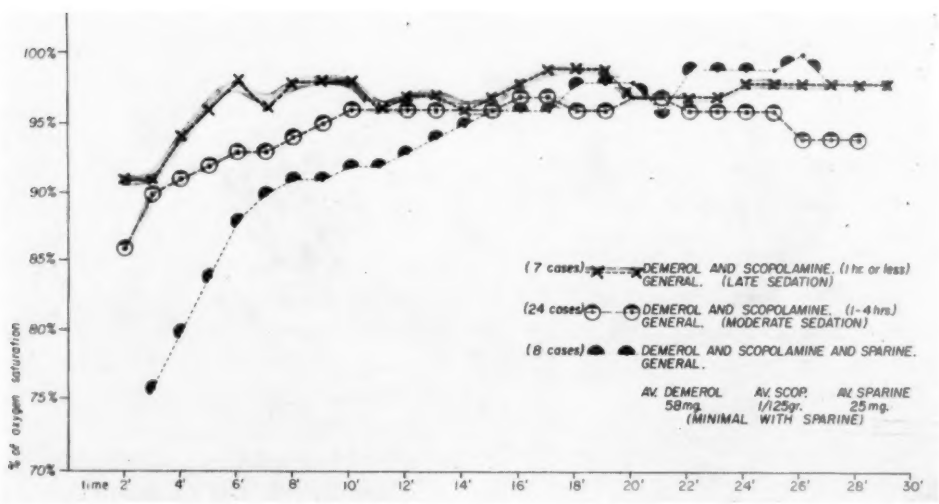


Fig. 4. The effects of Sparine when added to Demerol and scopolamine on labor.

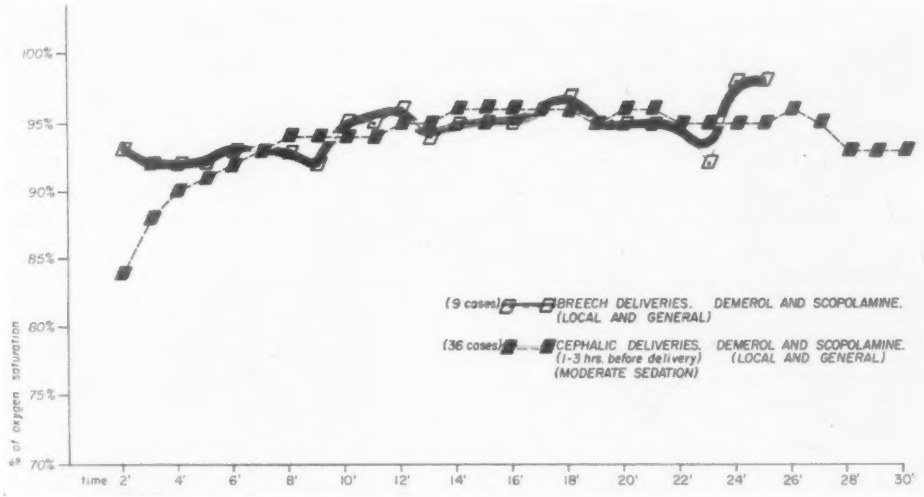


Fig. 5. A comparison of breech deliveries with cephalic deliveries.

esthesia were used in these groups. All babies of *uncomplicated* breech deliveries showed an oxygen saturation at 2 minutes after birth of over 90 per cent and remained at this level or above.

Fig. 6 compares Lorfan co-administered with moderate sedation and Lorfan administered 10 to 60 minutes prior to delivery. Both general and local anesthesia was used. This graph demonstrates that Lorfan given shortly before delivery results in slightly higher oxygen saturation.

Fig. 7 demonstrates the effect of major obstetrical complications on oxygen saturation in the newborn infant and also represents a summary of all other groups. In the presence of significant obstetric complications there is noted a marked diminution in initial and subsequent oxygen saturation in the infant. The prompt high oxygenations of the newborn infant after breech delivery and the prolonged lag in oxygenation of the repeat sedation group stand out. The remainder of the cases demonstrate the various

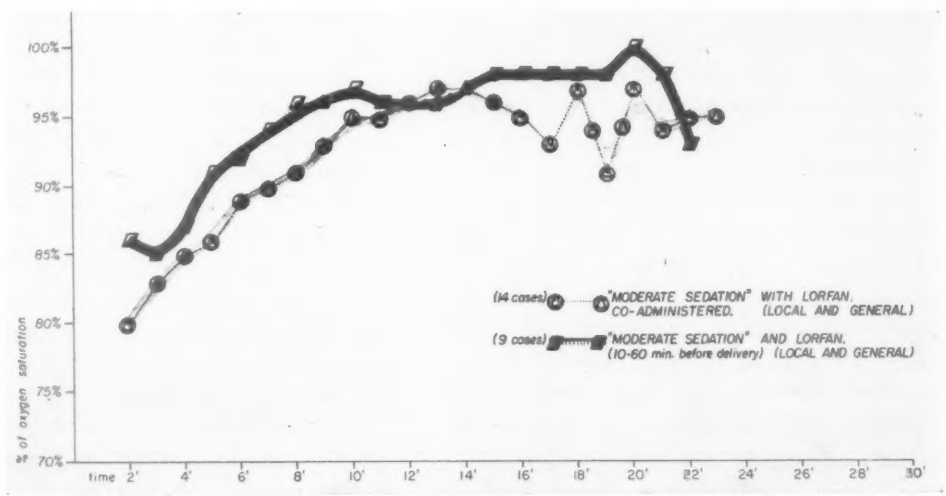


Fig. 6. The effects of Lorfan administered within one hour of delivery time.

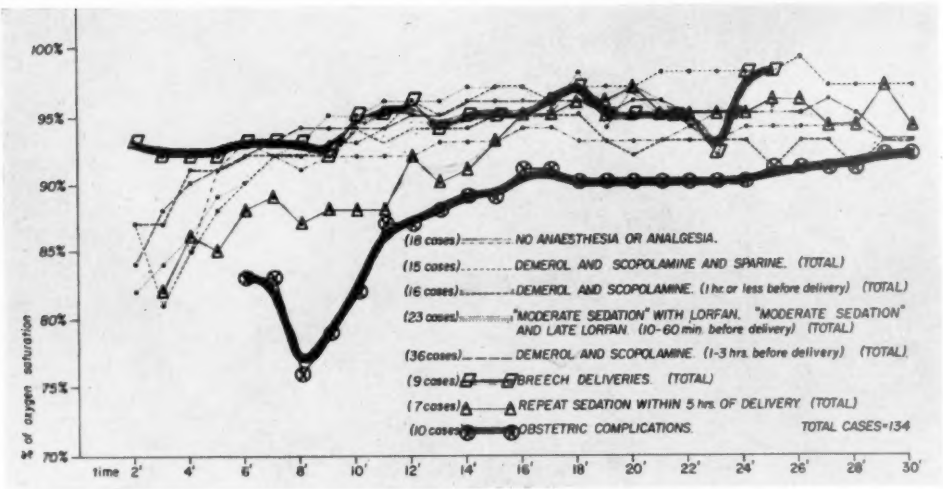


Fig. 7. A composite of the entire study, emphasizing the outstanding changes.

limits of difference of the groups evaluated.

Pediatric follow-up of all infants from all groups in this study revealed no evident variation in nursery behavior or developmental progress. In the "major obstetric complications" group, the infants were followed for 6 months. These infants developed normally and the observed depression in the oxygen saturation apparently caused no damage.

Comment

The ear oximeter has proved to be a useful tool with which to obtain data concerning the oxygen saturation of the peripheral blood. Although the values are not absolute, the percentage error is small in the range suitable for study of the newborn infant. It is a reliable instrument for comparative evaluation.

In general, in normal obstetrics, the judicious administration of sedative drugs and general anesthesia has no pronounced or lasting deleterious effect upon the newborn infant as reflected in the oxygenation of the peripheral blood and subsequent pediatric rating of the infant in hospital. In the group in which the obstetric complications occurred, a six month follow-up was made. All of these infants thrived and appeared normal. Certain observations of interest evolved from this study.

Sedation administered late in labor or repeated in labor does depress oxygen saturation in the newborn. This is of a low order, is transient, and has no measurable adverse demonstrable effect upon the infant.

Combining Sparine, a narcotic potentiator, with small amounts of sedation causes a diminution of oxygen saturation in the infant of moderate degree. This is in keeping with our over-all observation that drugs which sedate and depress the mother result in the same effect upon the infant. Sparine, administered with small amounts of Demerol, results in a relaxed, quiet, *depressed* mother; the respiratory rate and excursion is diminished, resulting in lowered oxygen tension in the mother and hence in the infant.

It was observed that administering Lorfan with moderate amounts of sedation shortens the duration of effectiveness of the sedative action. The rise to higher oxygen saturation levels in the infant is prompt. Lorfan seems to prove useful where late or repeat sedation is desirable. In fact, Lorfan administered shortly before delivery to sedated patients results in relatively higher oxygen saturation levels in the newborn infant.

Obstetric complications are the major factor in the diminution in oxygen saturation in the newborn. Sedative drugs may, of course, produce some additive effect where obstetric complications are encountered. Our

data suggest, however, that such drugs, when desirable or needed, can be administered judiciously with no evident harmful effect upon the infant.

General anesthesia (ethylene 80 per cent, oxygen 20 per cent) administered properly has no adverse effect upon the oxygen saturation of the newborn infant. MacKay's observation that nitrous oxide causes a marked diminution of oxygen saturation in the newborn infant is probably due to the fact that to obtain adequate obstetric anesthesia with nitrous oxide, more than 80 per cent of this agent must be administered in the mixture. This will lead to a relative hypoxia in the mother and infant. In our series of patients sedated late or heavily, the babies delivered under general anesthesia showed a higher oxygen saturation than comparable babies delivered under pudendal block. This seems to be directly related to the stimulus of the administration of a general anesthetic with adequate oxygen content; the respiratory rate and depth in the mother remains depressed under regional anesthesia; under general anesthesia the respiratory excursion is increased with a resultant increase in the oxygen saturation in the newborn.

In corroboration of the above observations it was noted in studies on the mothers that will be presented in a subsequent report, that under sedation there is a respiratory depression in the mother accompanied by a demonstrable decrease in oxygen saturation in the mother as determined by ear oximetry. A corollary observation on the mother showed that with each strong labor pain there was an increase in depth and rate of respiration with a concomitant rise in oxygen saturation in the mother. This rise lasted 30 to 60 seconds after the contraction. This may be a protective mechanism by which the fetus in utero may receive additional oxygen to compensate for the oxygen decrease alleged to occur because of the uterine contractions. In addition, this indicates the reason why drugs which depress the mother result in lower oxygen saturation in the mother and, therefore, in the infant.

The search must continue for drugs which will provide for a measure of relief of the discomfort in labor, but will not depress the respiratory rate and amplitude of the mother or directly affect the respiratory function of the newborn infant at birth.

Uncomplicated breech delivery revealed an interesting fact. In this group, the oxygen saturation within two minutes of birth was consistently over 90 per cent. This is in contrast to the relatively lower oxygen concentrations in which the presentation was cephalic, even compared to the group in which no sedation was used. This indicates to us that intrauterine oxygen saturation is higher than we have heretofore been led to believe and the forces of labor in the cephalic presentation during the birth process cause diminution in the oxygen saturation of the infant at birth.

These observations may cause us to question some of the long accepted, but never proved, concepts of intrauterine physiology. For instance, may we not imply that it is the birth process that depresses oxygen saturation rather than that the fetus is in a relatively hypoxic state throughout gestation? Perhaps the high hemoglobin levels in the infant in utero exist for reasons other than relative hypoxia.

The earlier studies on oxygen saturation in the newborn which were carried out on cord blood are probably invalid. Cord blood does not reflect accurately the oxygen saturation in the infant at birth. The birth process in cephalic presentation depresses oxygen saturation in the newborn. The cord blood studies measure the situation in the cord, not in the infant.

These findings correlate with Pennoyer's observations, referred to above, that fundal pressure causes reduction in the oxygen saturation of the infant at birth and that there is no correlation between cord oxygen saturation and behavior patterns in the newborn. We observed, in a few recent cases studied, that compression of the fetal head, even after birth, produces a measurable depression of the peripheral oxygen tension. Perhaps the fetus is not on Everest after all.

Summary

One hundred and thirty-four cases were studied, and the literature on oxygen saturation in the newborn was reviewed and correlated. The ear oximeter was found to be an accurate instrument for comparative studies of peripheral oxygen saturation, and the effects on the newborn of various analgesic and anesthetic agents, as reflected in the peripheral oxygen saturation, were evaluated.

Conclusions

1. Peripheral oxygen saturation levels represent one measurable facet of the status of the newborn.

2. Intrauterine oxygen levels are higher than has heretofore been described.

3. The judicious use of analgesic and anesthetic agents does not adversely affect the newborn.

4. Respiratory depression in the mother is reflected in reduced oxygen saturation in the newborn.

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Discussion

Dr. James H. McClure, Chicago, Illinois. The oxygen environment of the human fetus in utero on the one hand, and shortly after its birth on the other hand, is poorly understood despite many attempts at clarification. This is completely understandable since collection of suitable specimens of blood of the prenatal human infant is virtually impossible. Specimens can be obtained at birth, both at cesarean section and at vaginal delivery, before the child takes the initial breath. Recently a technique for blindly inserting a needle during late pregnancy through the intact maternal abdominal wall into the subplacental lake has come into common use. Obviously this can be done *only* when the placental insertion is anterior.

In addition to the almost impossible task of collection of blood samples, there is the difficulty of analytical methods underlying all studies of blood oxygen. Different methods give different

results on the same blood sample. All methods need to be standardized in relation to the time-consuming Van Slyke analysis. Even then many experimental errors creep in. Studies checked and cross-checked by various methods have greater validity than those relying upon a single method. The worth of each study must be appraised in relation to all factors involved. Thus, there *is* "doubt cast . . . on the measurement of oxygen saturation and its accuracy" obtained by a single method.

I was confused as I read the authors' discussion and summary concerning which conclusions were reached following their study of the literature and their own experimentation. They assail the numerous gasometric studies leading to the "Mt. Everest in utero" concept and state that "the ear oximeter is an accurate instrument for comparative studies of peripheral oxygen saturation." The crux of the experimental data presented here relates to the accuracy of the method. What is the error inherent in the use of the infant earpiece and the Waters direct reading oximeter? I shall limit my comments to the method. An excellent review of direct oximetry is to be found in *Methods In Medical Research,* Volume 2, Year Book Publishers, Inc., Chicago, Illinois.

The oximeter used in this study is a production model of a modification of the oximeter developed by Wood and associates—I say "production model" because those of you who have had recent encounters with new automobiles, television sets, and other electronic appliances understand only too well American manufacturers' quality control. The earpiece used in this study is called "infant" because it is a miniature version of the larger "adult" earpiece. To calibrate the instrument accurately would require simultaneous oximeter readings and manometric determinations of per cent oxygen saturation of arterial blood with the Van Slyke manometric blood gas apparatus or a method which has been checked against the Van Slyke method. Indeed, the manufacturer's instructions state that "although these instruments can be used for direct measurement of blood oxygen saturation, an initial empirical calibration against manometric determinations of blood oxygen saturation is necessary. . . ." With the exception of the work done by Howard and his colleagues, the calibration data mentioned in this review were obtained with either an adult or infant earpiece on *adult* ears. The data reported by Wood and others, and by Broch and Haarsted were apparently obtained with different oximeters. A careful examination of the graph presented by Howard's group does not permit an answer to our question concerning accuracy. They do, however, note that "during the period of blood collections from the heel prick, oximeter readings varied over a range of 10 per cent. . . ." I hasten to add that no paper entitled "Newborn Oxygen—The Psychosomatic Approach" has been published. It may be concluded from Howard's data that a 15 per cent oximeter error can exist (10 per cent because the infant's feelings are hurt and 5 per cent oximeter-gasometric analysis difference). Optical glass filters are supplied with the instrument for a day to day check but no data have been published to support filter use as a substitute for repeated manometric calibration.

An attempt lasting 2 years in my laboratory to calibrate the *Water's direct reading double scale oximeter with infant earpiece* (said to be more accurate than the single-scale) against the Van Slyke apparatus was totally unsuccessful. Even an hour to hour filter check could not be obtained with this particular instrument. The pressure capsule of the earpiece failed because of faulty design. Despite many telephone consultations and several returns of the earpiece to the factory for replacement or repair, we have never been able to calibrate the instrument against manometric gas analysis.

With such an experience behind us we abandoned this instrument as unreliable for oxygen analysis of the newborn and returned to the cumbersome manometric methods of gas analysis.

DR. S. R. M. REYNOLDS, Chicago, Illinois. Anesthesia early in labor is a clinical problem. However, we established with the tokodynamometer some years ago what every obstetrician knows, namely, that anesthesia early in labor may depress uterine contractions.

The question of the newborn infant's having low oxygen tension for a few months after birth is one that might seem to cause some alarm but I think the record which Dr. Rubovits has shown indicates results that are not necessarily severe. The subsequent history of the babies show no differences in the several groups. They did well.

I would like to mention the question of fetal anoxia and what may be said about a depressed heart rate in the fetus. In one particular experiment we did on fetal lambs in utero a maneuver was carried out that raised the maternal arterial pressure but had slight effect on the pressure in the inferior vena cava. The intrauterine pressure

did not vary much. The effect on the fetal circulation is evident. As passive congestion in the placenta continued by virtue of the elevated aortic pressure, the fetal heart rate slowed. This is a physiological response which may be prevented by supplying oxygen to the mother and so to the fetus. The fetal cardiac output is not substantially reduced since fetal arterial pressure holds up well.

Another experiment indicated a situation in which there was a depression in maternal respiration, in venous pressure, and in aortic pressure during hypoxia. Again, the fetal heart rate slows, but fetal arterial and venous pressures hold up well.

In another experiment there was but a slight depression of maternal respiration. The fetal heart rate held up for a while. In this case a heart block occurred. Almost any cardiovascular change in the mother will cause a decrease in fetal heart rate which is not indicative of fetal distress.

Some question has been raised about the state of the oxygen tension and saturation of the blood of the fetus in utero. This was referred to recently by Eastman as "Everest in utero," an expression coined by Bancroft. This situation is not true, however. It is true that the oxygen tension is low and oxygen saturation is lower than in the mother; there is a change in the blood pH. However, if a pregnant ewe is acclimatized at 18,000 feet altitude, there is actually increased content and increased saturation of fetal blood relative to maternal blood because the fetus develops a full acclimatization response. If, therefore, the fetuses were in a situation comparable to that at the top of Mt. Everest, it would present a far different blood picture than it does. The fetus is not hypoxic in utero, but rather under physiological conditions that are normal for it, but not for the mother, or for us! This work was carried out by Dr. Kaiser of Minnesota, at Illinois. Interestingly enough, at an altitude of 18,000 feet these subjects developed polycythemia.

DR. COOPERMAN (Closing). We knew of the trouble Dr. McClure was having with the oximeter. We heard of this long ago. We can only say, do not buy a cheap instrument. The one we bought cost $700, not $350. This instrument of ours has been used effectively by us as well as by many other investigators. It has been used widely, and no one to my knowledge has experienced the difficulties that Dr. McClure was beset with. Substantiation of absolute readings may be somewhat difficult to obtain, but there is always an intern around who can be used as a control. If, in a preliminary control test, the oxygenation is found to be between 90 and 100 per cent, the instrument is considered "in order," and measurements on the newborn are an accurate description of what is happening.

In so far as percentage of error is concerned, in the upper limits (90 to 100 per cent oxygenation) the error is considered to be 4 to 5 per cent.

As far as the comments of Dr. Reynolds concerning anesthesia in labor, I wish to state that general anesthesia, properly administered, may be a factor in the better oxygenation of the depressed mother.

As to the comment that various hemodynamic changes, other than maternal respiration, can alter oxygenation, I feel this is perfectly true. However, with women in labor where the fetal dynamics remain relatively constant in any short period of time, we have demonstrated to our own satisfaction that changes in maternal respiration of any magnitude will affect oxygen saturation in the newborn.

CURRENT OPINION

Re-evaluation

Report of the Maternity Center Association Clinic, 1952-1958

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THE Maternity Center Association of New York recently terminated its home delivery service, which was organized in 1932 as part of the Nurse-Midwifery Clinic. A previous report by Laird[1] in 1955 covered the period from 1932 to 1951. During that time the Maternity Center Association Clinic registered 6,884 patients for home delivery. This present report covers the period from 1951 to the close of the Clinic in 1958. During this time 1,548 patients were registered for home delivery.

There are many points of similarity between the first MCA Clinic report and the second report, and there are some interesting differences. The Clinic began about the time of the famous report of the New York Academy of Medicine on maternal mortality.[2] The Clinic thus began at a time of greatly increased interest in maternal care and it made significant contributions to the improvement of that care for a number of women in New York City. The Clinic maternal mortality rate for the period 1932 to 1951 was 0.88 per 1,000 live births. The rate for the whole period of the Clinic's existence from 1932 to 1958 was 0.86 per 1,000 live births. For the sake of reference it is noted that New York Hospital reported a rate of 1.2 per 1,000 live births for the years 1932 to 1956.

During the years covered by this second report there has been a shift in emphasis of maternity care toward a more enlightened concern for the fate of the child. By 1951 the maternal mortality rate had been reduced below the so-called "irreducible minimum" envisaged by the Academy of Medicine report of 1932. Now the fetal and neonatal mortality rates came under greater scrutiny. In the light of this change of emphasis, this second report of the MCA Clinic presents the fetal and neonatal deaths in some detail.

As indicated before, immediate service was rendered to patients by nurse-midwives in connection with the Nurse-Midwifery School. They consisted of supervisors, staff, and pupils. Associated with the service were 4 obstetricians who were engaged in teaching, medical supervision of prenatal and postpartum clinics, and emergency service. The Nurse-Midwifery School is under the control of the Maternity Center Association, which, in turn, has a medical board of outstanding obstetrical teachers. Tables I to IV give a survey of the work of the Clinic.

The one maternal death occurred in a

patient aged 31, gravida iv, para ii, whose last menstrual period was May 2, 1956, and whose first Clinic visit was Dec. 4, 1956. Her history was noncontributory and a physical examination was essentially normal at the 2 Clinic visits. At the second visit on Dec. 18, 1956, the height of the fundus was 23 cm. and the baby was found to be in the right occipitoanterior position. At 8:30 A.M. on December 29, a call was received that the mother was in distress. When the physician arrived at the patient's home at 9 A.M., she was found to be dead. The Medical Examiner reported "multiple massive pulmonary embolizations; pulmonary infarctions secondary to thrombosis iliac veins. Contributory, seven and one-half months' pregnancy." In a personal communication the Chief Medical Examiner stated that this was the first such death in his experience.

Tables V and VI show the weights of the total number of babies and also of the babies who accounted for the fetal and neonatal deaths.

Included in the total of 29 fetal deaths is a group of 9 in which the weight of the fetus was less than 1,000 grams. They are excluded from review not only because of weight, but because (1) their average time under clinic care was too brief to survey adequately, (2) information from the hospital giving care was often incomplete, or (3) information from the patient could not be secured. This confirms a study by Baumgartner and associates[3] on the inadequate reporting of early fetal deaths in New York City, despite a Department of Health regulation. This lack of information is particularly noteworthy in view of the zeal with which the investigators for this report followed up all possible leads. The total experience with regard to all babies

Table I. Total registrations accepted for home care by the MCA medical service

Disposition of registrants			*No.*	*%*
Dismissed pregnant (because of social and/or economic reasons, although approved medically for home care)			214	14
Delivered at home		1,128		73
By nurse-midwives	99.6%			
By physicians	0.4%			
Hospitalized for medical reasons		206	1,334	13
Total registrations			1,548	100

Table II. Total pregnancies terminated in home and hospital

	Place of delivery		
	Home	*Hospital*	*Home and hospital*
No. mothers*	1,128	206	1,334
No. mothers with multiple pregnancy	5	10	15

*Incidence of unmarried mothers, 8 per cent.

Table III. Total births (live births and fetal deaths) in home and hospital

Births	*Home*	*Hospital*	*Home and hospital*
Live births	1,124	196	1,320
Fetal deaths	9	20	29
Stillbirths	9	13	22
Early abortions (500 grams)	0	7	7

Table IV. Births and fetal, neonatal, and maternal deaths by number and rate

	Home	*Hospital*	*Total home and hospital*	*Rates**	
				Per 1,000 births	*Per 1,000 live births*
Total births†	1,133	216	1,349		
Live births	1,124	196	1,320		
Fetal deaths	9	20	29	21.50	21.96
Neonatal deaths	8	8	16	11.87	12.12
Maternal deaths	1	0	1	0.74	0.76

*Gross fetal and neonatal death rate per 1,000 births, 33.36. Gross fetal and neonatal death rate per 1,000 live births, 34.08.
†Includes multiple births: at home 5, in the hospital 10, total 15.

Table V. Total births

*Weight (grams)**	*Home*	*Hospital*	*Total*
0- 200	0	4	4
200- 299	0	3	3
300- 499	0	1	1
500- 999	3	10	13
1,000-1,499			
1,500-1,999	7	10	17
2,000-2,499	50	26	76
2,500-2,999	223	48	271
3,000-3,999	753	95	848
4,000-4,999	96	14	110
5,000 plus			
Weight not determined	0	5	5
1 full term died undelivered	1	0	1
Total	1,133	216	1,349

*Incidence of prematurity (under 2,500 grams) in this series was 8.5 per cent.

Table VI. Gross fetal and neonatal deaths

	Home			*Hospital*			*Total*		
*Weight (grams)**	*Fetal*	*Neonatal*	*Total*	*Fetal*	*Neonatal*	*Total*	*Fetal*	*Neonatal*	*Total*
0- 200				4	0	4	4	0	4
200- 299				3	0	3	3	0	3
300- 499				0	1	1	0	1	1
500- 999				2	1	3	2	1	3
1,000-1,499	1	0	1	1	4	5	2	4	6
1,500-1,999	4	0	4	2	1	3	6	1	7
2,000-2,499	2	3	5	3	0	3	5	3	8
2,500-2,999	0	2	2	2	1	3	2	3	5
3,000-3,999	2	2	4	2	0	2	4	2	6
4,000-4,999	0	1	1	1	0	1	1	1	2
5,000 plus	0	0	0	0	0	0	0	0	0
Total	9	8	17	20	8	28	29	16	45

*Seventy-one per cent of the fetal and neonatal deaths were of premature infants (under 2,500 grams); one fourth of these were abortions (under 500 grams). Five sets of twins were born in the home and survived; 10 sets of twins were born in the hospital, 3 of the babies died: Twin A, 1,200 grams, died under 24 hours, 2 weeks of antepartal care; Twin B, 1,260 grams, died under 24 hours, 2 weeks of antepartal care; Twin B, 1,200 grams, died under 48 hours, footling breech, 10 weeks of antepartal care. One in 5 had 20 weeks or more of antepartal care; 1 in 3 had 8 weeks or less of antepartal care.

Table VII. Fetal deaths of infants over 1,000 grams—home deliveries

Patient	*Age*	*Parity*	*Gravidity*	*Rh*	*Serology*	*Hemoglobin level*	*Obstetric history*	
							Past	*Present*
A. T.	33	2	2	+	–	11.8	1 living	Antepartum fetal death
G. N.	17	0	1	+	–	11.5	—	Normal
J. R.	15	0	1	+	–	10	—	Normal
I. M.	31	3	4	+	–	11	3 living	Normal
T. G.	26	0	1	+	–	12.5	—	Dermoid cyst
L. F.	40	6	7	+	–	11.5	6 living	Hydramnios
D. C.	26	3	5	+	–	11	3 living	Normal
H. R.	28	3	7	+	+	10	2 living	Antisyphilis treatment in full
T. R.	30	5	6	+	–	13	3 living	Hydramnios

Table VIII. Fetal deaths of infants over 1,000 grams—in hospital

Patient	*Age*	*Parity*	*Gravidity*	*Rh*	*Serology*	*Hemoglobin level*	*Obstetric history*	
							Past	*Present*
G. R.	33	1	2	+	–	11.5	1 living	Breech or transverse
L. D.	33	7	8	–	–	11.2	7 living	Breech, no titers
A. L.	29	1	2	+	–	11.5	3 living	
C. C.	20	1	2	+	–	12.2	1 living	AP bleeding
L. R.	30	1	2	+	–	10.7		Pre-eclampsia
V. J.	24	5	6	–	–	12.5		Hydramnios, titer 1/160
M. M.	19	2	4	+	+	11.5		Premature rupture of membranes
C. C.	18	0	1	+	–	12.5		Pre-eclampsia
A. G.	35	8	10	+	–	10.5	7 living	External version at 27 weeks
J. H.	24	3	5	+	–	11.5	2 living	Premature rupture of membranes
G. B.	23	3	5	+	–	10.2	3 living	Premature separation placenta

Prenatal care	*Gestation*	*Remarks*
18 weeks 15 visits	36	Normal spontaneous delivery, macerated 1,550 gram infant; no fetal heart sound 4 weeks; patient 3 years later had blood pressure 154/98
10 weeks 5 visits	35	Normal spontaneous delivery, 1,875 gram infant; anomalies of eyes and lip
2 weeks 2 visits	29	Precipitate delivery, 1,250 gram infant; polydactylism
3 weeks 2 visits	30	Died undelivered; see report
14 weeks 5 visits	30	Normal spontaneous delivery, 1,750 gram infant week following operation, removal dermoid
16 weeks 8 visits	38	Assisted breech delivery, 2,300 gram infant, spina bifida, hydrocephalus
12 weeks 6 visits	30	Normal spontaneous delivery (born before physician arrived), 1,550 gram macerated infant; 2 previous babies premature
20 weeks 11 visits	40	Normal spontaneous delivery, 3,350 gram infant; fetal heart sounds lost in labor; fetal liver much enlarged
22 weeks 10 visits	36	Normal spontaneous delivery, 2,000 gram anencephalic infant; previous baby had spina bifida

Prenatal care	*Gestation*	*Remarks*
11 weeks	40	Midforceps, 3,350 gram infant; impacted shoulders
25 weeks	40	Assisted breech, 4,000 gram macerated infant; premature rupture of membranes
11 weeks	40	Normal spontaneous delivery, 2,460 gram infant; tight, short cord
13 weeks	34	Normal spontaneous delivery, 1,860 gram infant; premature separation
20 weeks	36	Normal spontaneous delivery, 2,180 gram gram infant.
20 weeks	40? 40	Normal spontaneous delivery, 1,600 gram macerated infant; history of large babies
8 weeks	33	Normal spontaneous delivery, 2,180 gram infant
10 weeks	36	Normal spontaneous delivery, 2,200 gram macerated infant, after 2 weeks
25 weeks	42	Normal spontaneously delivery, 3,250 gram macerated infant; amnionitis
27 weeks	42	Precipitate delivery, 2,770 gram infant after Pitocin stimulation; rupture of uterus, hysterectomy
5 weeks	36	Normal spontaneous delivery, 2,500 gram infant

Table IX. Neonatal deaths of infants over 1,000 grams—home deliveries

Patient	*Age*	*Parity*	*Gravidity*	*Rh*	*Serology*	*Hemoglobin level*	*Obstetric history*	
							Past	*Present*
C. R.	22	1	2	+	-	11.4	1 living	Chicken pox
R. R.	19	0	1	+	-	12		—
P. R.	36	5	6	+	-	11.5	5 living	—
J. S.	38	6	7	+	-	11.5	6 living	—
M. S.	31	1	2	+	-	10		
J. R.	32	5	6	+	-	11.5	5 living	
A. C.	18	0	1	+	-	11.8		Breech
R. F.	24	3	4	+	-	10.5		

Table X. Neonatal deaths of infants over 1,000 grams—in hospital

Name	*Age*	*Parity*	*Gravidity*	*Rh*	*Serology*	*Hemoglobin level*	*Obstetric history*	
							Past	*Present*
P. B.	26	2	4	+	-	11.8	1 living	Breech, poor pelvis
C. C.	21	1	3	+	-	12	1 living	Premature rupture of membranes
A. F.	34	3	5	+	-	10.2	3 living	Twins
E. P.	24	1	2	+	-	10.5	1 living	Twins
N. N.	18	1	2	+	-	10.4	1 living	Antepartum bleeding

over 1,000 grams can then be summed up in Tables VII to X.

The concept of the "irreducible minimum" is not readily tenable when applied to vital statistics. We have seen what happened with maternal mortality rates in the past 20 to 30 years. But a careful review of the factors involved in our fetal and neonatal deaths suggests that few results might have been altered by different handling and that few might have been altered by the place of delivery, whether at home or in hospital. In the report by the MCA staff for its medical board, the question was posed whether or not perinatal and maternal mortality rates of a home and hospital service were comparable to those achieved in an exclusively hospital service. Figures were secured from the New York Hospital report of 1956[4] and compared with the Maternity Center Association Clinic reports of 1932-1951 and 1952-1958 (Table XI).

Prenatal care	*Gestation*	*Remarks*
13 weeks 11 visits	40	Baby breastfed; cleared with Department of Health epidemiologist; died twelfth day bilateral pneumonia, viremia in hospital
19 weeks 11 visits	39	Normal spontaneous delivery, 2,200 gram infant, upper respiratory infection in hospital Premature Unit
18 weeks 11 visits	40	Normal spontaneous delivery, 4,200 gram infant, medical examiner autopsy death due to aspiration
9 weeks 8 visits	40	Normal spontaneous delivery, 2,600 gram infant, hospitalized suspected purpura; died from gastroenteritis
13 weeks 7 visits	36	Normal spontaneous delivery, 2,300 gram infant, hyaline membrane, in hospital
3 weeks 3 visits	38	Normal spontaneous delivery, 3,200 gram infant, spina bifida, hydrocephalus
22 weeks 13 visits	36	Normal spontaneous delivery, 2,100 gram infant, apnea, bradycardia, lived 16 minutes
25 weeks 14 visits	40	Normal spontaneous delivery, 3,500 gram infant, oligohydramnios; immediate condition good; died in hospital 8 hours later from "atelectasis"

Prenatal care	*Gestation*	*Remarks*
13 weeks 8 visits	34	Cesarean section, 2,650 gram infant, tracheoesophageal fistula
2 weeks 2 visits	30	Assisted breech, 1,175 gram infant, died 4 days, had premature separation and stillbirth year before
10 weeks 8 visits	28	Normal spontaneous breech delivery; second twin, 1,200 grams, died 2 days
2 weeks 1 visit	26	Normal spontaneous delivery, both 1,200 grams; died less than 24 hours
8 weeks 7 visits	30	Normal spontaneous delivery, 1,600 gram infant, died 3 days

Summary

The concluding report of the Maternity Center Association Clinic covering the years 1951-1958 is submitted. It is briefly discussed in relation to the prior report of 1932-1951 and it is found that there are no marked changes in the type of patients cared for or in services rendered. In her report, Laird stated the conditions under which the Clinic was conducted then and these conditions continued in operation until its termination. She also asked some questions about the role of such a service in attracting well-qualified nurses into obstetrics, in improving doctor, nurse, and family interrelationships, and in improving patient-teaching. We believe that this nurse-midwifery service has played a significant role in all these endeavors, and we now ask if it has not also been able to achieve results in maternal and perinatal mortality comparable to a fine teaching hospital.

Table XI

	Years	*Rate per 1,000 births*	
I. Perinatal mortality comparison			
New York Hospital			
	1932-1950	29	(excludes infants under 1,500 grams)
	1951-1955	28	(excludes infants under 500 grams)
	1956	26	(excludes infants under 500 grams)
Maternity Center Association			
First report	1932-1951	52	(includes all products of conceptions*)
Second report	1951-1958	33	(includes all products of conceptions)
Corrected for comparison with New York Hospital data			
First report	1932-1951	42.8	(excludes infants under 500 grams)
Second report	1951-1958	28	(excludes infants under 500 grams)
II. Maternal mortality rates per 1,000 pregnancies			
New York Hospital	1932-1956	1.2	
Maternity Center Association	1932-1958	1.0	

*Complies with the law in New York City which requires the reporting of all products of conception.

Conclusions

1. The report of the Maternity Center Association Clinic for the years 1951-1958 is submitted.

2. Detailed analysis is made of fetal and neonatal deaths of infants over 1,000 grams in a combined home delivery and hospital service.

3. Comparison is made of perinatal and maternal mortality results achieved by this service and by a controlled hospital service.

4. With the conclusion of this combined home and hospital delivery service we might also ask what implication this report might have for nurse-midwifery in an all-hospital situation. It would seem at least that nurse-midwifery as a discipline could offer a good deal to the improvement of obstetric care in our hospitals.

I wish to record my thanks for all the help rendered by the director and staff of the Maternity Center Association Clinic for their help in preparing this report, and in particular to Miss Hemschemeyer for her valuable suggestions.

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Promazine as an adjunct to analgesia and sedation in labor

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IN JANUARY, 1956, the first known use of promazine hydrochloride as an adjunct to analgesia in labor was undertaken by the author and an associate, and the results were reported in detail in a preliminary publication.[1] Our findings were further borne out by Sprague[2] in a report which appeared about the same time. Several additional series[3-6] have since been carried out, and a similar combination also has been advocated for use prior to operation under regional anesthesia.[7]

Our criteria for satisfactory obstetrical sedation analgesia include: '(1) no respiratory or cardiovascular depression in the infant; (2) no deleterious effect (as circulatory, respiratory, or central nervous system disturbance) in the mother; (3) adequate alleviation of emotional tension and obtundation of pain; (4) no interference with the normal mechanism of labor; (5) no incompatibility with accepted anesthetics or other agents required during labor and delivery; (6) retention by the patient of sufficient command of her mental faculties to permit satisfactory response to instructions; (7) rapidity of action; (8) ease of administration.

Patients and procedures

Labor was conducted in 360 patients (120 primiparas, or 33 per cent; 240 multiparas, or 67 per cent of the group). All were admitted at term. Parity ranged from 0 to 11. Approximately 90 per cent had received antepartum care. Before the onset of labor, 26 (about 7 per cent) were mildly toxemic (systolic blood pressure ranging from 130 to 160 mm. Hg). No cases involving serious complications were included.

Medication. At first it was thought that one specific combination would suffice for all patients. This did not prove feasible, however. Several variations of the combination were considered desirable (Table I). All patients received the medication by intravenous injection. All agents used in each case were mixed and injected in the same syringe. When scopolamine was included it was the last component added to the mixture. Thirteen patients received pentobarbital sodium, 100 to 200 mg., as an oral medication. Seventeen, whose total labor lasted longer than 10 hours, required a second dose of meperidine of 25 to 100 mg.

Cervical *dilatation* at time of the injection was 2 to 6 cm. in 85 per cent, and 7 to 9 cm. in 15 per cent. The over-all average dilatation was 5 cm.

Sixty-four per cent received the injection one to six and one-half hours after the onset of regular contractions (Table II). Strong contractions were occurring every 1 to 3 minutes in 53 per cent, and moderate pains every 3 to 5 minutes in 42 per cent. Four per cent were experiencing mild contractions at intervals greater than 5 minutes, and for 1 per cent the rate of contractions was not charted.

From the Marian Pavilion, St. Mary's Hospital.

Table I. Predelivery medication and dose administered

Total dose administered intravenously	*Patients*	
	No.	*% of total series*
Promazine, 50 mg., meperidine, 50 mg.	216	60
Promazine, 50 mg., meperidine, 50 mg., scopolamine, 0.4 mg.	111	31
Second dose of meperidine, 25 to 100 mg.	17	5
Promazine, 50 mg., meperidine, 50 mg., pentobarbital sodium, 100 to 200 mg.	13	3
Dosage not recorded	3	1
	360	100

Table II. Relationship of medication to onset and duration of labor

Time dose administered after onset of active labor			
Hours		*% of total patients*	*% of primiparas*
Less than 1 (5 to 45 min.)		16	6
1 to 3		24	65
3½ to 6½		40	
7 to 15		18	27
17 to 31 (2, 17 hr.; 3, 24 hr.; 1, 31 hr.)		2	2
Duration of labor after medication			
Hours		*% of total patients*	*% of primiparas*
Less than 1 (15 to 58 min.)		22	3
1 to 3		52	89
3½ to 6½		22	
7 to 14 (6, 7 hr.; 1, 9 hr.; 4, 11 hr.; 1, 13 hr.; 1, 14 hr.)		4	8
Total duration of labor			
Primiparas			
Minimum	1 hr., 5 min.	Average—5 hr., 41 min.	
Maximum	29 hr., 15 min.		
Multiparas			
Minimum	44 min.	Average—5 hr.	
Maximum	31 hr., 45 min.		

The subjective and objective evidence of *sedation-analgesia* in the mother was graded according to the criteria described in our previous report.[1] The effect of medication was considered *excellent* when the patient became quiet and relaxed immediately after the initial intravenous dose, slept or dozed throughout labor, showed little or no appreciation of the contractions, and on the first postpartum day reported slight or no memory of the events prior to administration of the anesthetic. The result was graded as *good* if the patient became relaxed and somnolent after the injection, but was more or less aware of some of the contractions. These patients usually stated that the pain became less intense after the medication and that they were not unduly disturbed by any of the experiences they remembered. In all others in whom the sedative-analgesic response was less pronounced than those described above, the result was considered *fair* (Tables III, A and III, B).

The maternal *blood pressure* and *fetal heart* rate were determined every 5 minutes from the time promazine was administered until delivery, and the maternal blood pressure was taken every 15 minutes for 1 to 2 hours in the recovery room.

Anesthesia. The usual anesthetic was a combination of nitrous oxide, oxygen, and ether. A large number of deliveries were

accomplished under nitrous oxide and oxygen only, even in cases in which episiotomy was done and forceps were used.

Results

The results obtained in this series closely paralleled those of the first study.

Twenty-two per cent of the patients were delivered in less than one hour, and 74 per cent in one to six and one-half hours after the injection. (Table II).

The average total duration of labor, in the primiparas, was 5 hours, 41 minutes; in the multiparas, 5 hours. Normal spontaneous delivery occurred in 75 per cent of the total series (58 per cent of the primiparas), and low forceps were used for 23 per cent (41 per cent of the primiparas). There were 4 footling breech deliveries (1 per cent). Breech extraction was performed in 3 cases (1 per cent). Episiotomy was done in 49 per cent.

Fifteen patients (4 per cent of the total series) vomited after the medication was administered. Eight of these had received pentobarbital sodium in the predelivery medication (61 per cent of the barbiturate-treated group).

All patients responded in some degree to the medication. The sedative-analgesic effect was good to excellent in 92 per cent of the series (Table III). The best results were obtained with the combination of 50 mg. promazine, 50 mg. meperidine, and 0.4 mg. scopolamine. (Five per cent of the patients required a second dose of meperidine.) The response was good to excellent in 98 per cent of the group who received these three agents (Table III).

In no case was the blood pressure reduced below normal levels. Vasopressors were never required. The fetal heart rate was not affected by the medication, and remained within the usually accepted limits of normal —120 to 160 beats per minute. Variations occurred, of course, in relation to the uterine contractions.

Infants. Since no midforceps rotations and deliveries or other unusually traumatic procedures were included in this series, none

Table III, A. Sedation analgesia obtained in 360 obstetrical patients

Sedative analgesic effect	*Total series*		
	No.	*%*	
Excellent	232	64	92
Good	99	28	
Fair	28	8	
Response not charted	1		

Table III, B. Results in relation to dosage

Total medication administered	*Sedation-analgesia obtained (percentage of dosage group)*		
	Excellent	*Good*	*Fair*
Promazine, 50 mg.; meperidine, 50-150 mg.; scopolamine, 0.4 mg. (128 patients)	80	18	2
Promazine, 50 mg.; meperidine, 50 mg. (216 patients)	51	39	10
Promazine, 50 mg.; meperidine, 50 mg.; pentobarbital sodium, 100 to 200 mg. (13 patients)	—	37	63
(Dosage not charted, 3 patients)			
Average duration of labor after injection	2 hr.	3 hr.	4 hr., 41 min.

of the infants showed respiratory depression and none required resuscitation except the 3 delivered by breech extraction. The vast majority breathed and cried spontaneously as soon as delivery was accomplished; the remainder, immediately after being put down in the carrier bassinet. There were no fetal or maternal deaths.

Side effects

One patient, with a history of multiple allergies, experienced some wheezing after the intravenous injection, but refused antiallergic treatment. Within 20 minutes all the asthmatic symptoms subsided. A few patients reported some dryness of the nasal and oral membranes. There was no sign of local irritation at the site of injection.

Comment

In this series, as in the initial study, intravenous administration of promazine successfully met all criteria for sedation-analgesia in labor. The dose must be individualized. No single dosage schedule can be advocated for all parturients because of the great variety of factors that influence the progress of labor and the response to medication; e.g., the differences in pain tolerance from patient to patient. A general dosage range has been found practical, however. The initial dose seems to be fairly well standardized at 50 mg. promazine and 50 mg. meperidine. An additional dose may be required occasionally, often a short time after the first. For example, a second injection of 50 mg. meperidine usually suffices.

In this series 16 patients received a second dose of 25 to 50 mg. meperidine, and in one the second dose was 100 mg. Thus, the total dosage for the entire series ranged from 50 to 150 mg. All received but one dose of 50 mg. promazine. The superior results obtained in the group who also received scopolamine were probably the consequence of enhancement of the amnesic effect.

Although all patients are anxious for relief of labor pain, a few of those in whom sedation and amnesia had been most pronounced afterward somewhat paradoxically expressed the wish that they had been permitted greater consciousness of the birth process. In contrast, many who had been delivered by others in the same period, under conventional medication, were openly envious of the somnolence and detachment of their promazine-treated companions.

The absence of hypotension and disturbance in fetal heart rate conforms to the findings of the initial study in this respect. Bolton and Benson[4] used the same medication intravenously, in similar dosage, for 71 patients, almost all of whom were delivered under spinal anesthesia. They considered significant a reduction of 20 mm. Hg in systolic pressure. It is notable that this occurred in only 10 patients, 2 of whom required use of vasopressors; and it was suggested that these 2 cases may have been instances of "vena caval syndrome." Wegryn and Marks[3] also used the same predelivery regimen in 100 patients delivered under spinal anesthesia and encountered no clinical hypotension at any time.

The one asthmatic reaction to the medication that occurred in this study bears out the suggestion[3] that such a response may be stimulated by intravenous use of the combination in patients who have a history of respiratory allergy. This may be a consequence of the adrenergic blocking action exerted by a number of the phenothiazine derivatives.

Summary

In an additional study of 360 uncomplicated obstetrical cases, a combination of promazine and meperidine, with or without scopolamine, was administered for sedation analgesia. The results closely paralleled those of the first series.

Sedation analgesia was good to excellent in 92 per cent, and fair (that is, a less pronounced response) in 8 per cent. The average duration of labor totaled about the same for both primiparas and multiparas—5 hours, 41 minutes, and 5 hours, respectively. The sedative-analgesic obviously caused no slowing of the contractions.

The dose must be individualized. The

initial dose is usually 50 mg. promazine and 50 mg. meperidine; addition of 0.4 mg. scopolamine improves the results, probably through the enhancement of the amnesic effect.

There was no maternal hypotension or disturbance in fetal heart rate.

Vomiting occurred in 4 per cent of the patients and was of vastly greater frequency in the patients who had received barbiturate.

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Reviews | Abstracts

Edited by
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Reviews of new books

Die zellkernmorphologisch Geschlechtserkennung in Theorie und Praxis. By Hermann Adolf Heinz Heidelberg, 1959, Dr. Alfred Hüthig. 30 marks.

This monograph on sex diagnosis by examination of cell nuclei, after the method of Barr, is very complete in its review of prior work and scientifically impressive in the original contributions by the author. It is divided into sections, the first on review of background, method for body cells, method for leukocytes, findings in animals, and interpretation. The second section deals with the author's own work on fetal tissues, early abortions, tumors, and sexual malformation.

It is unfortunate that a difficult style makes it hard even for a reader thoroughly conversant with German to absorb the information which this dissertation has in such great abundance. Still, in view of the relative newness of the subject, this is a useful compendium which points to clinical applications, in addition to giving the present theoretical status of this field.

Diseases of the Newborn. By A. J. Schaffer. 878 pages, 357 figures, 22 tables. Philadelphia, 1960, W. B. Saunders Company. $20.00.

Despite some exposure to the problems of newborn infants, it was at first a surprise to find that so voluminous a text was required to cover this subject. Schaffer's *Diseases of the Newborn* is a compendium of 878 pages, well organized and comprehensive. Like all texts, it can present only a selected view of controversial issues and is not altogether free from prejudice. For example, it is amusing that of the many controversies that surround the problem of feeding the premature infant, the author selects only one on which to take a firm stand. This is that low-fat mixtures are superior to those containing a full complement of fat, whereas this reviewer has been exposed for a good many years to the successful use of formulas containing a relatively high content of vegetable oils. But this and various others are small points. In the main the material is presented authoritatively on the basis of both personal experience and, considering the extensive nature of the text, on an impressively up-to-date coverage of the literature. This text, unlike most modern compendiums, represents the work of a single author. While some special points may suffer from this approach, the author justifiably claims that a text written solely from the point of view of the pediatrician confronted with the problems of the newborn has the merit that initial recognition of the numerous problems best handled by one more highly specialized must come from one with a broader view of the neonatal period. We believe this text has great merit and will find extensive use.

Our Obstetric Heritage—Story of Safe Childbirth. By Herbert Thoms, 164 pages, 19 illustrations. Hamden, Connecticut, 1960, Shoe String Press. $4.75.

The deep interest in the history of medicine which Dr. Thoms has shown in previous writings is again evident in this, his latest work. The events which contributed to the present level of safety in childbirth are presented in detail. The history of the forceps, the development of the cesarean section operation, obstetric anesthesia, and the fascinating story of the conquest of puerperal sepsis are included. Dr. Thoms has also written short biographies of the great teachers of obstetrics, with emphasis on the American teachers, stressing their contributions to obstetric knowledge and maternal welfare.

Since technical language and medical details have intentionally been kept to a minimum, the

book should have wide appeal for anyone interested in the marvelous discoveries which helped to make childbirth safe.

Colposcopie. By Jules Bret and Fernand Coupez. 270 pages, 121 figures, 2 color plates. Paris, 1960, Masson et Cie. 45.00 NF.

In a concise and lucid style the authors of this book deal with their topic in a remarkable manner. Not just a descriptive text, it deals with the pathology seen under the colposcope both as a gynecologist and a pathologist might see it, correlating microscopic pathology with colposcopy. Its chief merit, however, lies in the attempt of the authors to place in time the several pathologic pictures described, relating them to destructive and healing processes as well as the development of malignancies.

No attempt is made to praise colposcopy in favor of cytology, but rather to assign to each method its logical place in the gynecologist's armamentarium.

The illustrations are of the highest quality and contribute in making this small opus enjoyable and stimulating.

Medical, Surgical and Gynecological Complications of Pregnancy. By the staff of the Mount Sinai Hospital, edited by Alan F. Guttmacher and Jos. J. Rovinsky. 619 pages, 47 figures, 36 tables. Baltimore, 1960, Williams & Wilkins Company. $16.50.

This volume is truly a valuable supplement to the standard textbook on obstetrics. The list of contributors, of which there are 68, include directors of departments, as well as fellows, and represents an intensive conjoined effort to give more comprehensive care to the obstetrical patient. This is borne out in the preface where the editors describe the reorganization of the obstetrical outpatient department into 10 specialty clinics, each of which meets separately from the routine prenatal clinic and each of which is under the direction of one or more senior staff members of the respective specialty. These clinics are: cardiac, pulmonary, hypertensive-renal, diabetic, hematologic, neurologic, psychosomatic, obstetric-gynecologic endocrine, vaginitis, and varicose vein. The obstetric-gynecologic residents attend these special clinics, thereby broadening their own training as well as reflecting their increased knowledge in improved patient care. That this must be a stimulating organization for the extra obstetric-gynecologic services is the fact that the senior staff physicians who initiated the special clinics continue to direct them several years later. This organization may well be adopted by many other teaching institutions where the directors may be anxious to provide more complete and comprehensive medical care and to train obstetric-gynecologic residents to have a greater scope of all branches of medicine.

The book is divided into 14 sections. The first 4 are devoted to the cardiovascular-renal system, pulmonary system, gastrointestinal system, and eye, ear, nose, and throat. Surgical, gynecologic, neuropsychiatric, hematologic problems, endocrine disorders, dermatology, syphilis, infections, collagen disorders, malignancy, and genetic considerations include the remainder.

The final section, on genetic considerations, with particular reference to radiation, pregnancy and progeny, and congenital abnormalities, is very amply discussed and, as characterized throughout the volume, the references are numerous and those before 1950 are largely excluded.

This authoritative volume should most certainly be given a position of easy accessibility in the library of obstetricians and gynecologists.

On the Causation of Varicose Veins and Their Prevention and Arrest by Natural Means. T. L. Cleave. 39 pages. Baltimore, 1960, Williams & Wilkins Company. $2.50.

This refreshing little book is a companion to one already published on coronary disease. Medical practitioners and dieticians will find an interesting point of view in this evolutionary study of the reasons why varicose veins have become so common in Westernized people.

Dr. Cleave's contention is that the remarkable adaptation of all species to their natural environment and, in this instance, to their eating habits has produced a colonic cause of varicose veins. He believes that what is involved may only be a simple delayed rate of passage of the colonic contents as well as the more obvious condition of crude constipation. The result is that there is an increased rise of venous pressure in the lower limbs which may be very little and quite possibly intermittent together with a reduced rate of flow in the veins. The fact that varicose veins and femoral thrombosis are more common on the left side would support this theory.

The author states that treatment of the causative stasis in the bowel should lie in the restitution of fiber to the food and not in the use of aperients, and advice is given on how this can be done by the well-to-do and also by those who are not well-to-do.

Since nearly all writers agree that about 75 per cent of those who suffer from varicose veins are women, this essay should have considerable interest for the obstetrician and gynecologist.

Gynecological Urology. Edited by Abdel Fattah Youssef. 893 pages, illustrated. Springfield, Ill., 1960, Charles C Thomas, Publisher. $22.50.

This is one of the most comprehensive works on the subject of gynecologic urology yet published. Thirty-three contributors are represented, each discussing a subject on which he is a recognized authority. The topics are arranged under such general headings as "Anatomy Physiology and Pharmacology," "Genitourinary Fistulae," "Sphincter Incontinence of Urine," "Urological Diseases of Gynecological Significance," "Effect of Gynecological Conditions on the Urinary System," and "The Urinary System in Gynecological Surgery."

Several of the contributors have prefaced their thoughts on the current management with excellent historical reviews of the topic, and the illustrations are from their own original publications. Each chapter has its own list of references. Some subjects are discussed by 2 or 3 contributors, giving the reader the benefit of the experience and judgment of more than one individual.

Selected abstracts

The Lancet

Vol. 1, Feb. 27, 1960.

*Lewi, S., and Clarke, T. K.: A Hitherto Undescribed Phenomenon in ABO Hemolytic Disease of the Newborn, p. 456.

Lewi and Clarke: A Hitherto Undescribed Phenomenon in ABO Hemolytic Disease of Newborn, p. 456.

Based on the observation that erythrocytes suspended in an agglutinating serum sediment more quickly than those suspended in a compatible serum (Sander, F., and Sander, M.: Ztschr. Immunitätsforsch. 95: 268, 1939), the sedimentation rate of erythrocytes obtained from cord blood of infants with ABO hemolytic disease was studied. Because the sedimentation rate of cord whole blood is always very low, the blood was centrifuged, the plasma removed, and the cells washed three times in neutral phosphate-buffered isotonic saline solution. The packed red blood cells were finally suspended in a polyvinyl pyrrolidone (P.V.P.) medium and the sedimentation rate determined in Westergren tubes every 5 minutes. The 10 and 15 minute readings were of most interest.

Of 3,924 cord blood samples, 835 were incompatible in the ABO system with the mother's group (children affected by Rh hemolytic disease, stillborn babies, and children who died or left the clinic in less than 3 days were excluded). The distribution of incompatible children was as follows: mother O, child A, 416; mother O, child B, 147; mother A, child B or AB, 146; mother B, child A or AB, 126 instances.

The sedimentation of compatible red cells was fairly uniform and amounted to about 5 mm. every 5 minutes. The sedimentation of incompatible red cells varied greatly.

1. Greatly accelerated sedimentation rate (a fall of 90 mm. or more in 10 minutes). Eight instances were found, all were of mother O/child A. All the children had severe hemolytic disease. Four required exchange transfusion because of hyperbilirubinemia. Others had hyperbilirubinemia which did not reach a dangerous level.

2. Moderately accelerated sedimentation rate (the 10 minute reading did not show a clear delineation between the packed cells and those remaining in suspension; at 15 minutes a clear line of delineation had developed). This was found in 25 instances (mother O/child A, 13; mother O/child B, 2). In this group the incidence of jaundice was high (17 out of 25) but no anemia was noted. One case only re-

*These articles have been abstracted.

quired exchange transfusion because of a dangerously high bilirubin level; the others recovered spontaneously.

3. Normal or slightly accelerated sedimentation rate. In this group the incidence of jaundice was not higher than in the control group of ABO compatible children.

The phenomenon of rapid sedimentation of red cells was observed only in hemolytic disease due to ABO incompatibility. In compatible ABO children affected by Rh hemolytic disease the sedimentation rate was normal in 17 instances and only very slightly accelerated in 3 instances.

In this disorder where all the tests that have been proposed for rapid and early diagnosis are inaccurate the phenomenon of rapid sedimentation may prove to be of use.

David M. Kydd

March 5, 1960.

*Garrett, J. V., Giles, H. McC., Coombs, R. R. A., and Gurner, B. W.: Neonatal Purpura With Platelet Iso-Antibody in Maternal Serum, p. 521.

Garrett et al.: Neonatal Purpura With Platelet Iso-Antibody in Maternal Serum, p. 521.

On the day after a normal delivery a full-term male infant developed a generalized petechial rash followed by the appearance of ecchymotic lesions. During the next 4 days the lesions subsided and subsequent progress was uneventful. At no time was the spleen palpable. The platelets were found to be reduced to 12 and 7,000 per cubic millimeter. Within 2 weeks the platelets rose to 80,000 and within 2 months to 210,000 per cubic millimeter. The hemoglobin level and white count were normal. Although the mother had developed sufficient anemia to require transfusion during this and a preceding pregnancy and had had a miscarriage at 16 weeks in the first pregnancy, no other abnormalities were found in either the mother (blood group O, Rh positive, CDe/CDe, Kell negative, Fy[a+] or the father (blood group O, Rh negative, cde/cde, Kell negative, Fy[a+]). The baby's blood group was O, Rh positive, CDe/cde.

Upon test, the mother's serum did not contain red cell antibody against either the baby's or father's red cells. With the technique of Chalmers and associates (Brit. J. Haemat. 5: 225, 1959) positive mixed agglutination reactions were attained when platelets from the father and 10 normal people were tested, whereas no reaction was obtained when the mother's own platelets were tested. In one preparation leukocyte antibodies were demonstrated. No demonstrable antibodies against the father's red cells were found.

David M. Kydd

April 9, 1960.

*Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, V. M., and Wolff, O. H.: A New Trisomic Syndrome, p. 787.

*Patau, K., Smith, D. W., Therman, E., Inhorn, S. L., and Wagner, H. P.: Multiple Congenital Anomaly Caused by an Extra Autosome, p. 790.

Edwards et al.: A New Trisomic Syndrome, p. 787.

An infant girl, born by cesarean section because of disproportion and mild toxemia, was noted to have multiple deformities (odd-shaped head with wide occipitoparietal and narrow frontal diameters, broad flat bridge of nose, small triangular mouth, webbed neck, hypermobility of shoulders, short, partially webbed toes, congenital heart disease with a high ventricular septal defect, and other minor defects). The child's mother and father, aged 31 and 32, respectively, and brother, aged 6, were healthy. Between the births of her 2 children the mother had had 2 miscarriages. Shortly after birth this infant had cyanotic episodes and jaundice. The latter subsided but recurred at the age of 6 weeks. A laparotomy disclosed an enlargement of the liver, which on biopsy proved to be due to hepatitis, small but patent bile ducts, and normal ovaries. Despite transfusions, the child died 2 weeks later.

Cytologic studies of skin and muscles showed that the great majority of cells from both tissues contained 47 chromosomes. On the basis of careful analysis it was decided that there were 3 chromosomes that were indistinguishable from the No. 17 chromosomes of the normal complement. The sex chromosomes were XX. The most likely explanation was thought to be that the extra chromosome had arisen as a result of nondisjunction during gametogenesis in one of the parents and that the patient was therefore trisomic for the No. 17 chromosome.

The hepatitis was though to be fortuitous but the other abnormalities were thought to be consistent with the type of disorder to be expected from autosomal trisomy. This abnormality may denote a clinical syndrome as specific as Mongolism.

David M. Kydd

Patau et al.: Multiple Congenital Anomaly Caused by an Extra Autosome, p. 790.

An infant now 13 months old and still alive has the following known congenital defects: cerebral defect, anophthalmia, cleft palate, hare lip, simian creases, "trigger thumbs," polydactyly, capillary hemangiomas, heart defect (probably interventricular septal defect). Both parents were 25 years of age and healthy. This was the mother's first pregnancy.

Cells obtained from the bone marrow in both the right and left tibias were cultured. The chromosomes were counted and found to be 47 in number. Analysis showed that the sex chromosomes were XX. The extra choromosome belonged to the group of medium sized acrocentric autosomes. (Group D in the classification used.) Thus, of the 22 conceivably viable types of autosomal trisomics, 3 have been found. Of those that proved to be viable each may show a clinically distinguishable syndrome. Trisomy may become instrumental in establishing for the first time autosomal linkage groups in man.

David M. Kydd

April 23, 1960.

*Gate, J. M.: Fetal Mortality in Essential Hypertension, p. 901.

Gate: Fetal Mortality in Essential Hypertentension, p. 901.

A series of 73 patients who were discovered to have a blood pressure of 150/100 or more before the twentieth week of pregnancy was studied. Two of these patients believed to have chronic nephritis were excluded from the series.

These patients were treated by insistence on long periods of rest which usually involved admission to the hospital and sedation. A few patients with severe hypertension received antihypertensive drugs. Induction of labor before term was favored and the pregnancy was never allowed to progress beyond the expected date of delivery. Artificial rupture of the membranes was performed in 26 patients (37 per cent) and cesarean section in 15 (21 per cent). The indications for the latter procedure were severe preeclampsia, 6; severe hypertension, 3; elderly primigravida, 2; contracted pelvis, 1; diabetes mellitus, 1; previous cesarean section, 1; prolonged labor, 1.

The total fetal loss was 6 (8 per cent) (4 stillbirths, 1 neonatal death, and 1 pregnancy terminated at 20 weeks because of advancing hypertension [230/150] with retinal and renal changes). All the infants which were lost weighed less than 5 pounds.

Edema or albuminuria developed in 30 patients (42 per cent) and it was in this group that 3 of the 4 stillbirths occurred. There were no maternal deaths.

These results were compared with those of Browne and Dodds (J. Obst. & Gynaec. Brit. Emp. 49: 1, 1942) who found that only 32 per cent of the infants survived and no woman with a blood pressure of 180 mm. or over before the twentieth week bore a live child. The difference in the 2 series was attributed to the improvement in obstetrical care (insistence on rest, induction of labor before term, and increased use of cesarean section) and in the care of premature infants that has occurred during the last 20 years.

David M. Kydd

May 21, 1960.

*McAllister, R. A., Sim, A. W., Hobkirk, R., Stewart, H., Blair, D. W., and Forrest, A. P. M.: Urinary Estrogens After Endocrine Ablation, p. 1102.

McAllister et al.: Urinary Estrogens After Endocrine Ablation, p. 1102.

With the method of Brown (Biochem. J. 60: 185, 1955) estriol, estrone, and estradiol-17-β were determined in a group of women with inoperable or metastatic breast cancer before and after oophorectomy, adrenalectomy, or radioactive implantation of the pituitary. Response to these forms of therapy was accepted only when there was objective evidence of regression of tumor deposits. The mean estrogen levels in those patients whose cancers regressed did not differ significantly from those in whom no improvement occurred. Although lesser amounts of the estrogens were excreted after oophorectomy and adrenalectomy than after pituitary implantation there was no significant relation to the response to oophorectomy, adrenalectomy, or pituitary implantation.

David M. Kydd

May 28, 1960.

*Stanbury, J. B., and Chapman, E. M.: Congenital Hypothyroidism with Goitre p. 1162.

Stanbury and Chapman: Congenital Hypothyroidism with Goitre, p. 1162.

Among the immediate forebears of a boy of 15

there were 3 consanguineous marriages, and many instances of goiter occurred. The patient at an early age was discovered to have hypothyroidism. After the administration of thyroid extract he improved dramatically and his bony maturation became normal. When he was at the age of 15 the patient's mother noted that the boy was developing a goiter and stopped giving the thyroid medication. Within a month hypothyroidism became evident. The basal metabolic rate was −39 per cent. The total serum-iodine concentration was 1.5 μg per 100 ml. and the protein-bound iodine 0.5 μg. The serum cholesterol concentration was 320 mg. per cent. The sella turcica was possibly slightly larger than normal size but there was no erosion of the clinoids.

A biopsy specimen of the thyroid gland was found to contain numerous small nodules. Some were cystic but most were cellular. There were numerous cellular adenomas and intense hyperplasia. There was scarcely any colloid to be seen.

After the oral administration of I^{131} only 11.4 per cent was located in the thyroid gland after 24 hours and only 7.8 per cent after 48 hours, whereas 67.5 per cent of the I^{131} appeared in the urine within 24 hours and 85.3 per cent within 48 hours. Forty-eight hours after the I^{131} was given the concentration of labeled iodine in the serum was 0.40 per cent and that of protein-bound I^{131} was 0.041 per cent per liter. Chromatographic studies of the serum and urine showed that inorganic iodine was the only I^{131}-labeled substance.

In the saliva the concentration of iodide was not significantly different from that in the serum. Both parents, a sister, and a maternal aunt were studied also and the salivary : serum ratio of iodide was in each instance greater than 21 which was similar to the values obtained in control subjects. The ratio obtained for chlorides was normal but that for thiocyanate was low, indicating little if any concentration in the saliva although the serum value (0.4 mg. per 100 ml.) was normal. The ratio of I^{131} in gastric juice 5 hours after administration was 0.8. Renal clearance of I^{131} iodide was normal. Tissue slices obtained from biopsy material failed to accumulate I^{131}. Concentration of total and protein-bound iodine in a fragment of tissue were 4.43 and 4.23 μg per gram wet weight of tissue. Calculations based on these results showed that the total thyroid iodine was less than one quarter of the normal value.

Those results suggested that this patient lacked the ability to concentrate iodine in the thyroid gland and that this defect was responsible for the development of hypothyroidism. In view of the occurrence of many goiters in this consanguineous family and that the defect may be genetically linked it was disapponting not to find evidence of impaired salivary iodide secretion in other members of the family. The possibility that a dietary or endogenous metabolite having an effect similar to perchlorate might be responsible for the findings in this patient could not be excluded.

On the assumption that there was a defect in the trapping of iodide in the thyroid gland this patient was given 1 mg. potassium iodide three times daily. In 4 weeks his basal metabolic rate rose from −38 to −1 per cent. All the symptoms of hypothyroidism disappeared and the goiter diminished to about one third of its size at the time of the biopsy.

David M. Kydd

Vol. 2, Aug. 13, 1960.

*Bolton, J. H., Forester, F. M. C., and Kerley, L. F.: Free Lysine Excretion in Pregnancy, p. 345.

Bolton, Forester, and Kerley: Free Lysine Excretion in Pregnancy, p. 345.

The amount of lysine excreted in 24 hours was determined in 31 pregnant women by the chromatographic method of Kerley (J. Lab. & Clin. Med. 53: 149, 1959). The patients were divided into four groups: normal pregnancy (11); pre-eclampsia (9); placental insufficiency (3); and various other complications including urinary infection, anemia, labile hypertension, and threatened abortion (8).

The daily lysine excretion in 15 nonpregnant controls ranged from 0 to 50 mg. with a mean of 30 mg. Although considerable variation was encountered, in general in the first of three groups there was a rise to a maximum level at approximately 3 months followed by a gradual fall to delivery. Furthermore there was a difference between these three groups that could be detected as early as the sixteenth week. The three groups maintained their relative positions throughout with placental insufficiency showing the largest amounts of lysine being excreted (range at fifth month: 95 to 170 mg. per day) and normal pregnancy the lowest (range at fifth month: 16 to 74 mg. per day). In pre-eclampsia the range at the fifth month was 18 to 200 mg.

per day. In the fourth unspecified group lysine excretion was consistently low (range at the fifth month: 0 to 66 mg. per day). The authors suggest that increased lysine excretion in pregnancy may be related to certain pregnancy diseases. However, amino acid metabolism in pregnancy requires further investigation to avoid mere speculation.

David M. Kydd

Sept. 3, 1960.

*Anderson, M., Went, L. N., MacIver, J. E., and Dixon, H. G.: Sickle-cell Disease in Pregnancy, p. 516.

Anderson et al.: Sickle-Cell Disease in Pregnancy, p. 516.

Of 17 patients with various types of sickle cell disease who were followed through one pregnancy and were delivered at the University College Hospital in Jamaica, 9 had SS genotype, 7 had SC, and 1 had SF. Seven of the 9 patients with sickle cell disease (SS) had had symptoms of this disease prior to the pregnancy. One stillbirth occurred. All but one of the patients with this disorder were jaundiced. These patients developed acute symptoms of their disease during the course of the pregnancy, 4 developed acute symptoms during the postpartum period, and 1 additional patient had acute symptoms both during the pregnancy and postpartum. Three cesarean sections were required.

Among the 7 patients with sickle cell–hemoglobin C disease only one was jaundiced during the pregnancy and this patient developed a splenic infarct on the thirteenth day post partum. One other patient developed fever and joint pain in the postpartum period. The only other complications were an attack of slight joint pain at the thirty-eighth week in 1 patient. The one patient who had sickle cell–thalassemia (SF) was not jaundiced and had no complications beyond an episode of thrombophlebitis that occurred on the sixth day post partum. The average birth weight in this series was 5 pounds, 10 ounces for the children of mothers with sickle cell disease (SS) and 6 pounds, 9 ounces for those with mothers who had sickle cell–hemoglobin C disease (SC) as compared with an average figure for this hospital of 7 pounds, 4 ounces. These low birth weights do not appear to be related to prematurity. Mild pre-eclampsia arose in only 2 patients so that the possibility is raised as to whether erythrostasis of sickled red cells may not occur in the uterine and decidual arterioles.

With two exceptions these 17 patients were studied during a period in which there were 4,500 deliveries which gave an incidence of one case of sickle cell disease in 300 which approaches the incidence of these two disorders (SS and SC) in the general population (1 in 225). Thus, in Jamaica the incidence of the disease associated with pregnancy was higher than expected from previous reports for elsewhere and the incidence of complication especially among the SC group was lower. Complications were more frequent in the puerperium.

However, in an addemdum one patient who had sickle cell–hemoglobin C disease (SC) and who had no complications during the pregnancy reported in the present series subsequently became pregnant, developed a severe aplastic crisis and aborted. This crisis was as severe as anything seen in sickle cell disease (SS). It is of interest that 27 of the patients' children had aplastic crisis at about the same time.

David M. Kydd

New York State Journal of Medicine

Vol. 60, Sept. 15, 1960.

*Adair, F. E.: The Place of Radical Mastectomy, p. 2853.

Adair: Place of Radical Mastectomy, p. 2853.

The author reports that with radical mastectomy 54.4 per cent of operable cases of breast cancer are cured. If the cancer is confined to the breast the cure rate is 83 per cent and reduced to 47.2 per cent if there is spread to the axilla. As yet, no accurate clinical methods are available to determine the biologic type of the tumor or host resistance.

It is stated that simple mastectomy unnecessarily condemns those with limited axillary disease and that those who favor simple mastectomy are in the minority and have thus far reported only a small number of cases where there has been high selectivity. In the author's experience concerning 200 radical mastectomies performed in 1959 there was axillary involvement in 47.5 per cent of the cases. This is contrasted to 60 per cent axillary involvement in radical mastectomy cases 20 years ago, proving the value of routine periodic physical examinations. The author believes that a greater percentage of cures will be effected by an extension of the operation than by its limitation.

Reuben H. Adair

Correspondence

Volvulus after cesarean section

To the Editors:

On page 551 of the September, 1960, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, I read an article written by Alvin M. Siegler and Sol H. Rogatnick entitled "Cesarean Section Complicated Post Partum by Volvulus."

In this work 5 previous and similar cases were reported or mentioned.

In the Dec. 1, 1958, issue of the *New York State Journal of Medicine,* we (Drs. Stephen W. Giorland, Muny L. Krandt, and José Herrera) reported one case as "A Case of Volvulus of the Cecum Following Low Flap Cesarean Section."

In view of the fact that Drs. Siegler and Rogatnick do not mention our case, it may be of interest to do so at this time.

José A. Herrera, M.D.

Calle José Trujillo Valdez No. 135
Santiago, Dominican Republic
Oct. 28, 1960

Items

American Board of Obstetrics and Gynecology

The next scheduled examinations (Part II), oral and clinical, for all candidates, will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from April 8 through 15, 1961. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I examination will be notified of their eligibility for the Part II examinations as soon as possible.

Current bulletins of the American Board of Obstetrics and Gynecology, outlining the requirements for application, may be obtained by writing to the secretary.

Robert L. Faulkner, M.D.
2105 Adelbert Road
Cleveland 6, Ohio

Annual prize award of Central Association

The Central Association of Obstetricians and Gynecologists offers an annual award of $500 for outstanding investigative or clinical work in the field of obstetrics and/or gynecology.

Those eligible to compete are accredited physicians, teachers, research workers, and medical students living within the geographic area of the Association.

Papers should be written expressly for this competition, and they must be original, not having been previously presented or published.

Manuscripts must be submitted to the secretary, in triplicate, and must reach him not later than July 5, 1961. The author's identity shall not show on any of the 3 copies, the only identification being a covering letter and an abstract not to exceed 150 words.

The cash award and a Certificate of Merit will be presented to the successful author at the annual meeting of the Association. The paper shall be included as part of the Scientific Program at the annual meeting Oct. 5, 6, and 7, 1961, at Cleveland, Ohio. The paper will be offered for publication with the transactions of the Association.

Communications with regard to the award should be made to Herman L. Gardner, M.D., secretary, 6436 Fannin Street, Houston 25, Texas.

Central Association of Obstetricians and Gynecologists

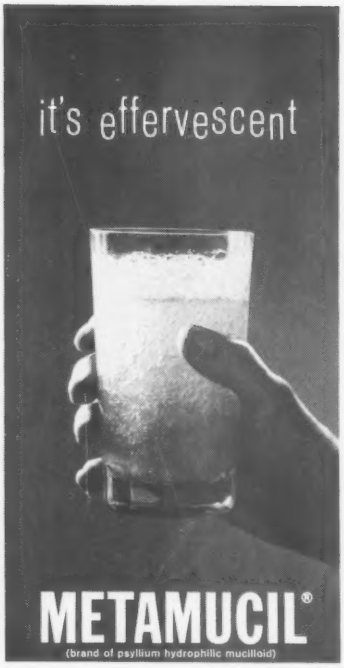
The next annual meeting of the Central Association of Obstetricians and Gynecologists will be held in Cleveland, Ohio, Statler-Hilton Hotel, Oct. 5, 6, and 7, 1961.

The scientific program will be presented on each morning of these dates, and, on the afternoon of October 6, the Cleveland Obstetrical Society will present a special scientific program.

All accredited physicians, residents, and interns are invited to attend, without registration fee. Further information can be obtained by writing the secretary, Herman L. Gardner, M.D., 6436 Fannin Street, Houston 25, Texas.







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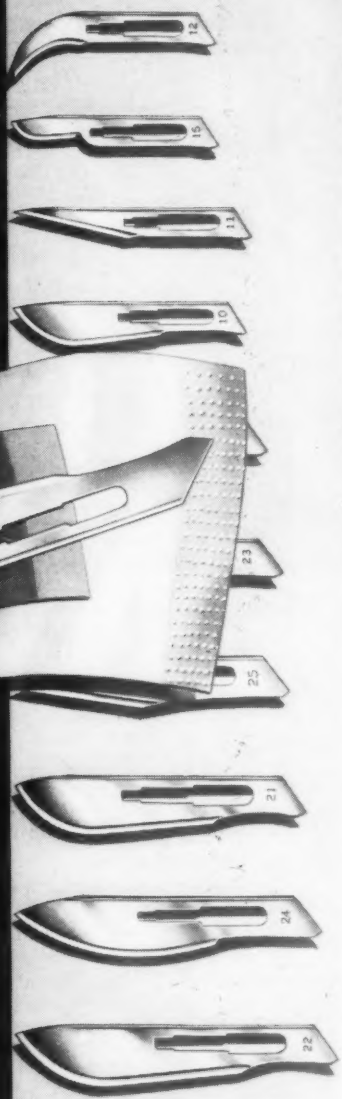


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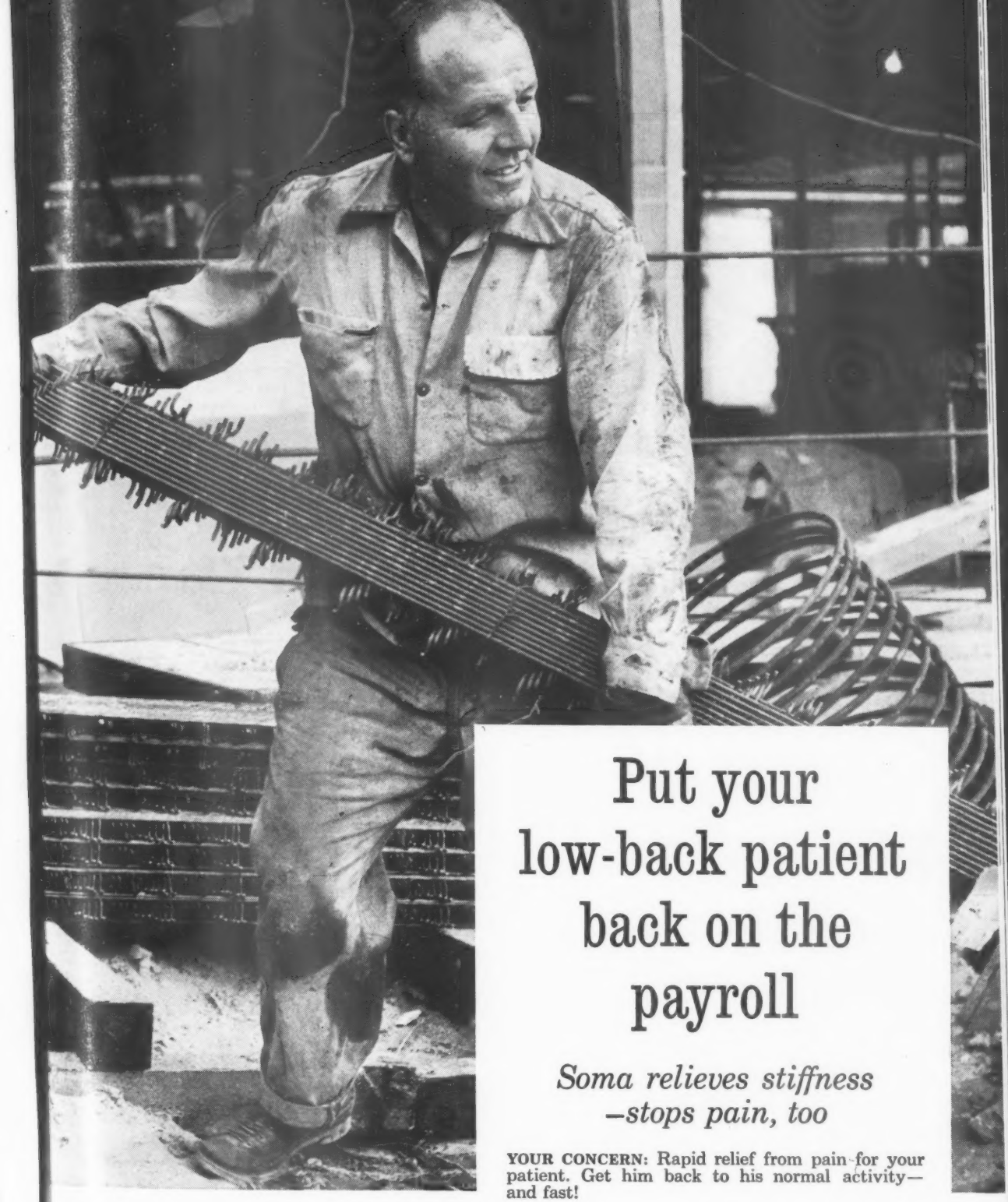


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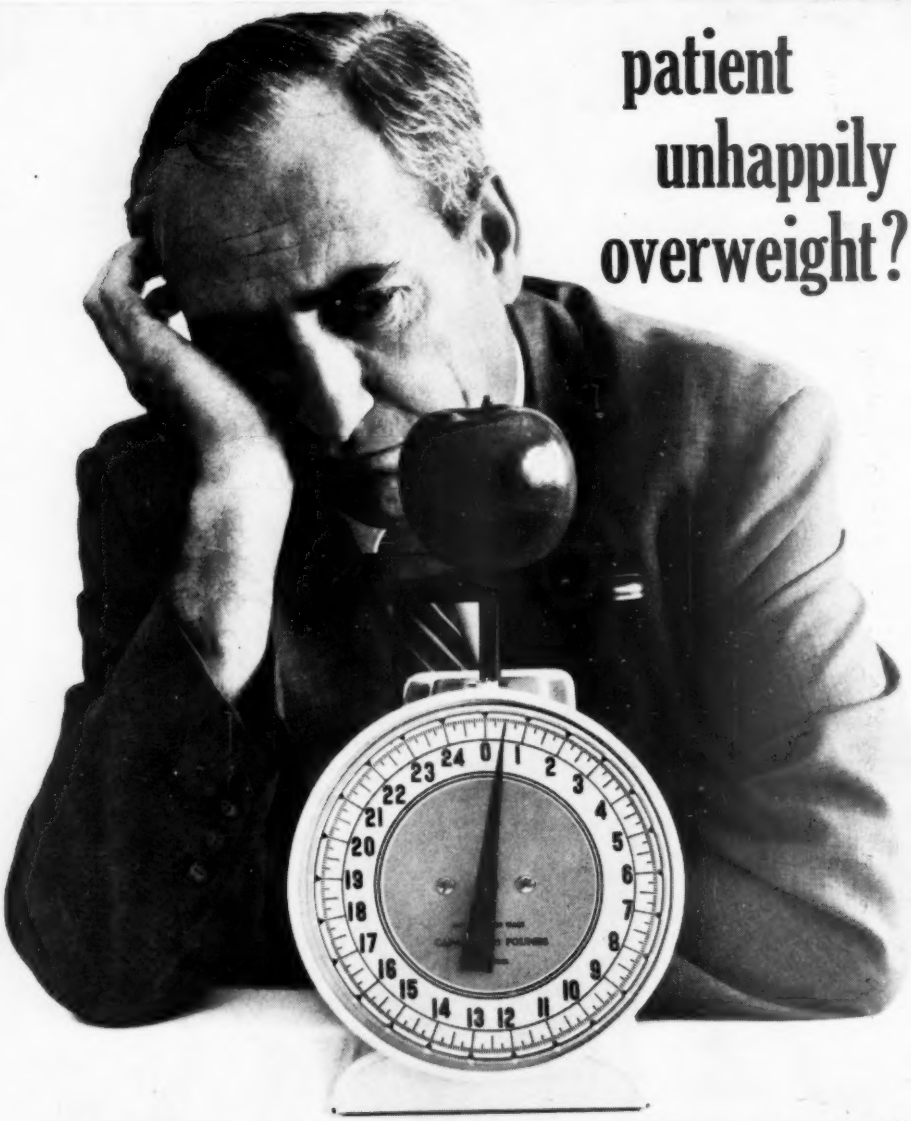
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[1] Douglas, H. S.: West. J. Surg. 59:238 (May) 1951.

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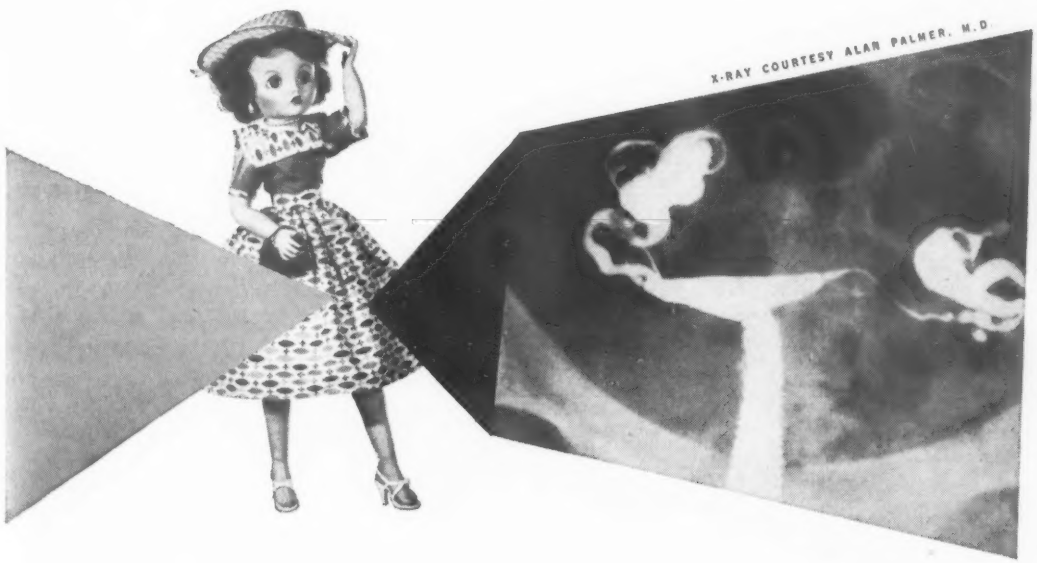
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2. Palmer, A.: Internat. J. of Fertil. 4:365 1959



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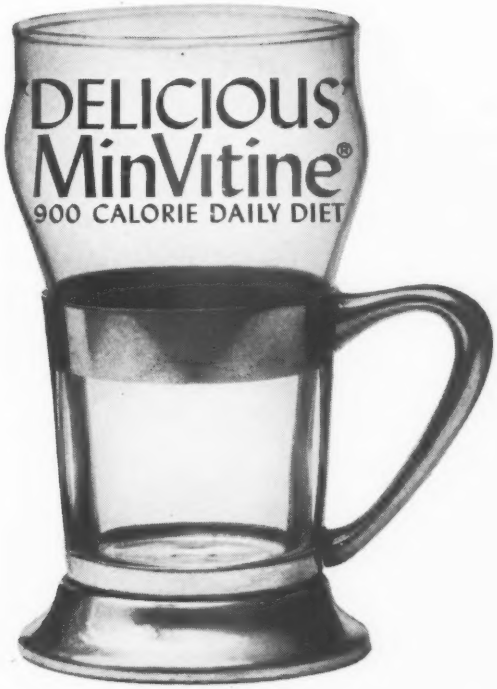
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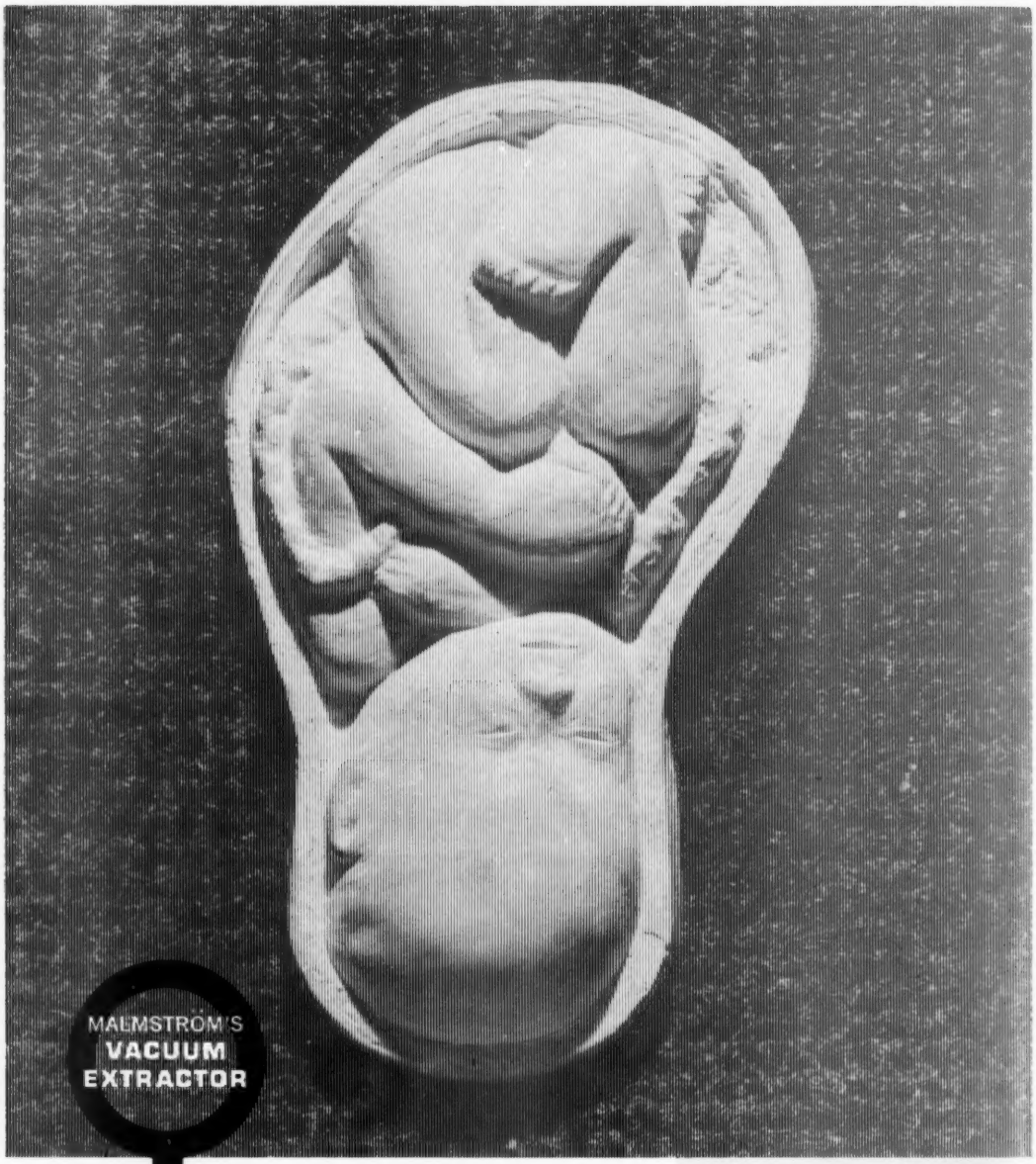


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*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1959, p. 661.

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As *Powder:* 5 oz. Plastic Insufflator Bottles; *As Vaginal Inserts:* Boxes of 24. NOTE: Consult package circular for full details on instructions for use of both Powder and Vaginal Inserts.

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*Patent Applied For.

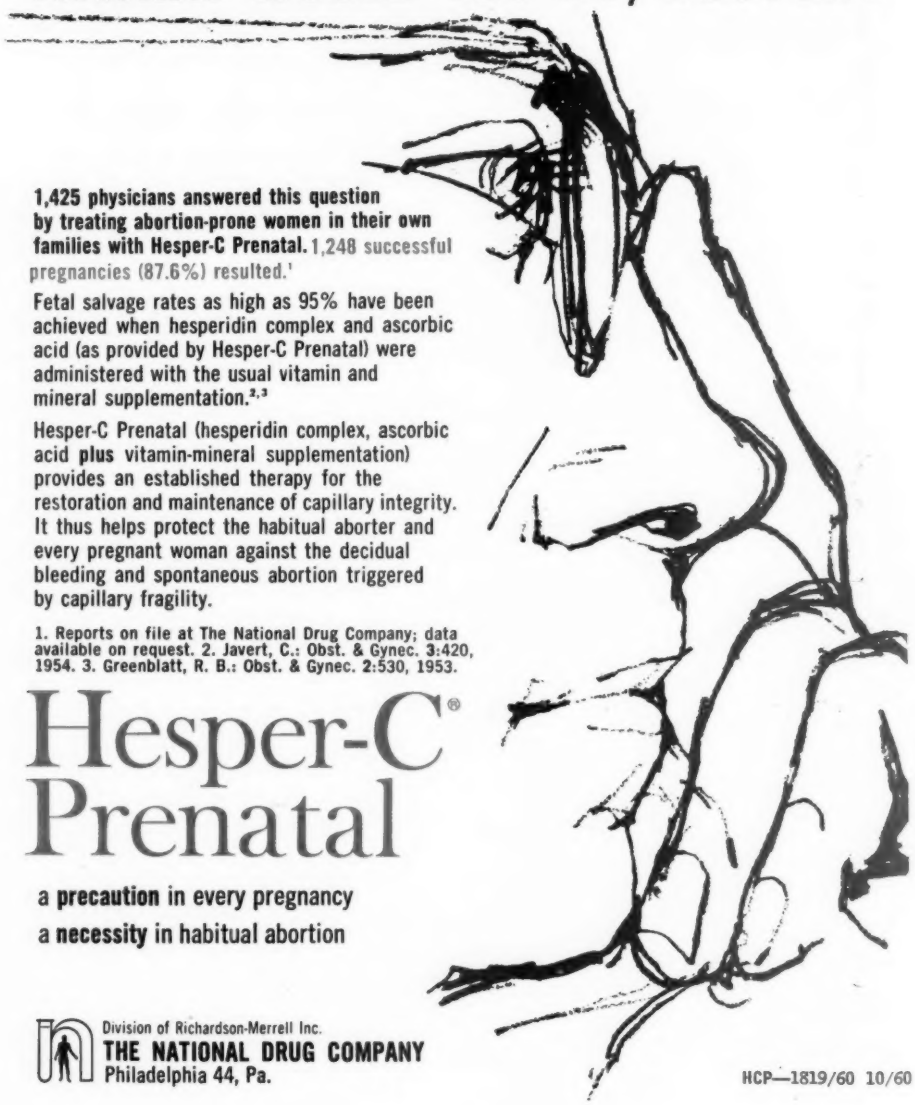
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1. Reports on file at The National Drug Company; data available on request. 2. Javert, C.: Obst. & Gynec. 3:420, 1954. 3. Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953.

Hesper-C® Prenatal

a **precaution** in every pregnancy
a **necessity** in habitual abortion

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Control weight gain from test to term

Rx the anorexic with no reported contraindications

TENUATE suppresses appetite with no effect on heart rate, blood pressure, pulse or respiration,[1] no alteration of BMR.[2]

In a recent study of 105 patients who used diethylpropion (TENUATE) throughout their pregnancies,[3] the following effects on weight were recorded:

Actual loss of weight..... 7 patients
No gain in weight.....11 patients
Gain of less than 3 pounds per month....55 patients
Gain of more than 3 pounds per month..32 patients

DOSAGE: One 25 mg. Tablet one hour before meals, or 1 *new* TENUATE DOSPAN Tablet (75 mg.) daily, in midmorning, swallowed whole. An additional 25 mg. Tablet may be taken in midevening to control nighttime hunger.

SUPPLIED: TENUATE Tablets (25 mg. each), bottles of 100 and 1000; TENUATE DOSPAN Tablets (75 mg. each), bottles of 100.

REFERENCES: 1. Alfaro, R. D.; Gracanin, V., and Schlueter, E.: J. Lancet, *In press*. 2. Huels, G.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 3. Nulsen, R. O.: Cur. Therap. Res. 2:102, 1960. 4. Horwitz, S.: Personal communication, 1959. 5. Spielman, A. D.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 6. Ravetz, E.: Michigan Acad. Gen. Pract. Symposium, 1959. 7. Decina, L. J.: Exper. Med. & Surg., *In press*. 8. Scanlan, J. S.: Personal communication, 1959. 9. Kroetz and Storck: Personal communication, 1959.

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hunger control with less than 1% CNS stimulation[2,4-9]

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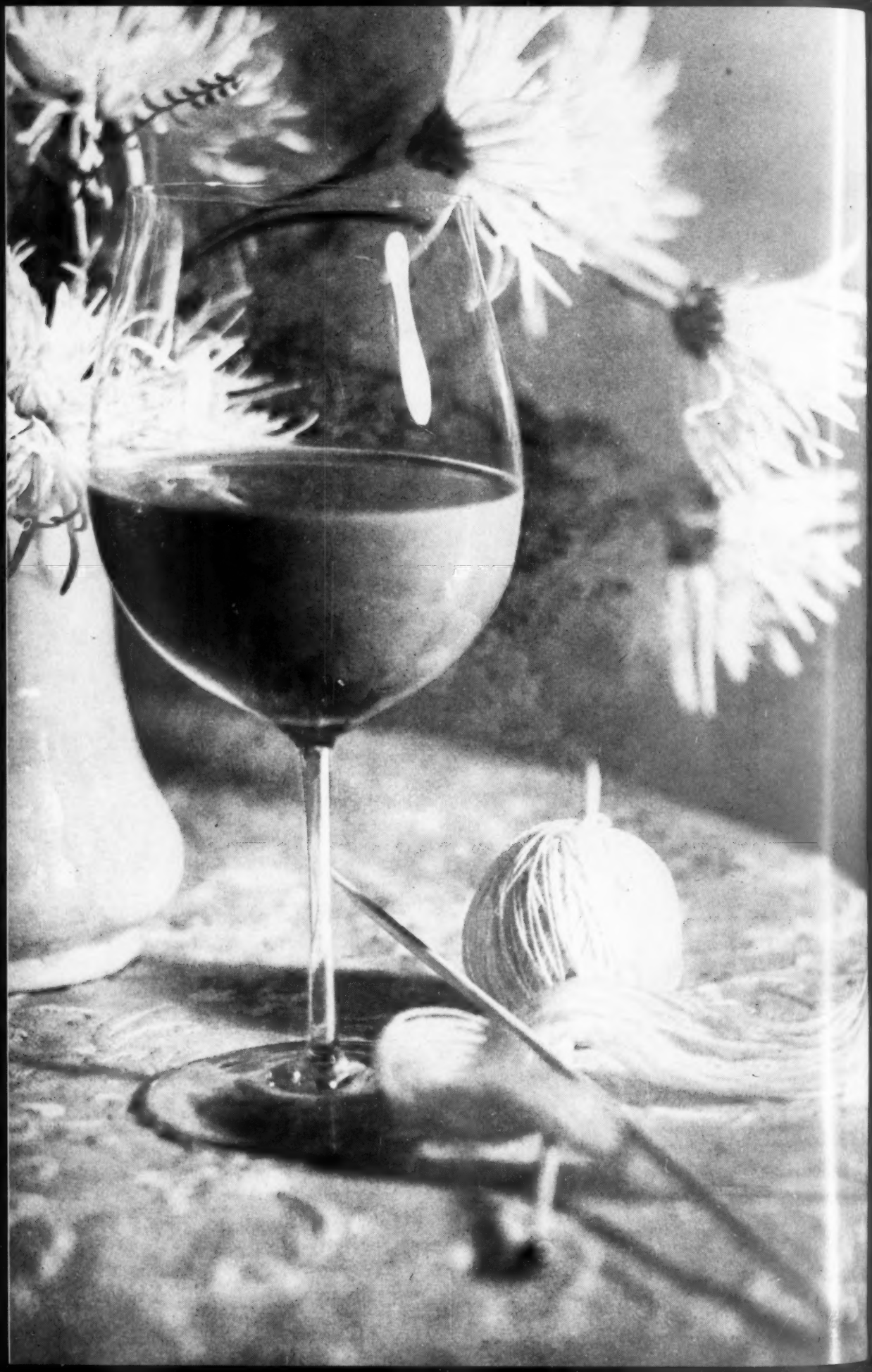
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references: (1) Taller, H.: The Problem of Obesity, Am. J. Obst. & Gynec., *78*:1144-1148 (Nov.) 1959. (2) Antos, R. J.: The Use of a New Dietary Product (Metrecal) for Weight Reduction, Southwestern Med. *40*:695-697 (Nov.) 1959. (3) Tullis, I. F.; Allen, C. E., and Overman, R. R.: Simple Effective Weight Reduction: A Clinical Study, Scientific Exhibit, 6th Internat. Cong. Int. Med., Basel, Switzerland, Aug. 24-27, 1960. (4) Roberts, H. J.: Effective Long-Term Weight Reduction—Experiences with Metrecal, accepted for publication.

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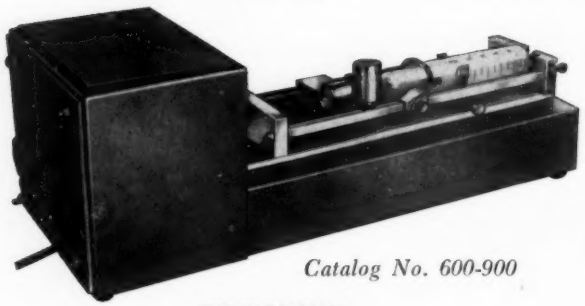
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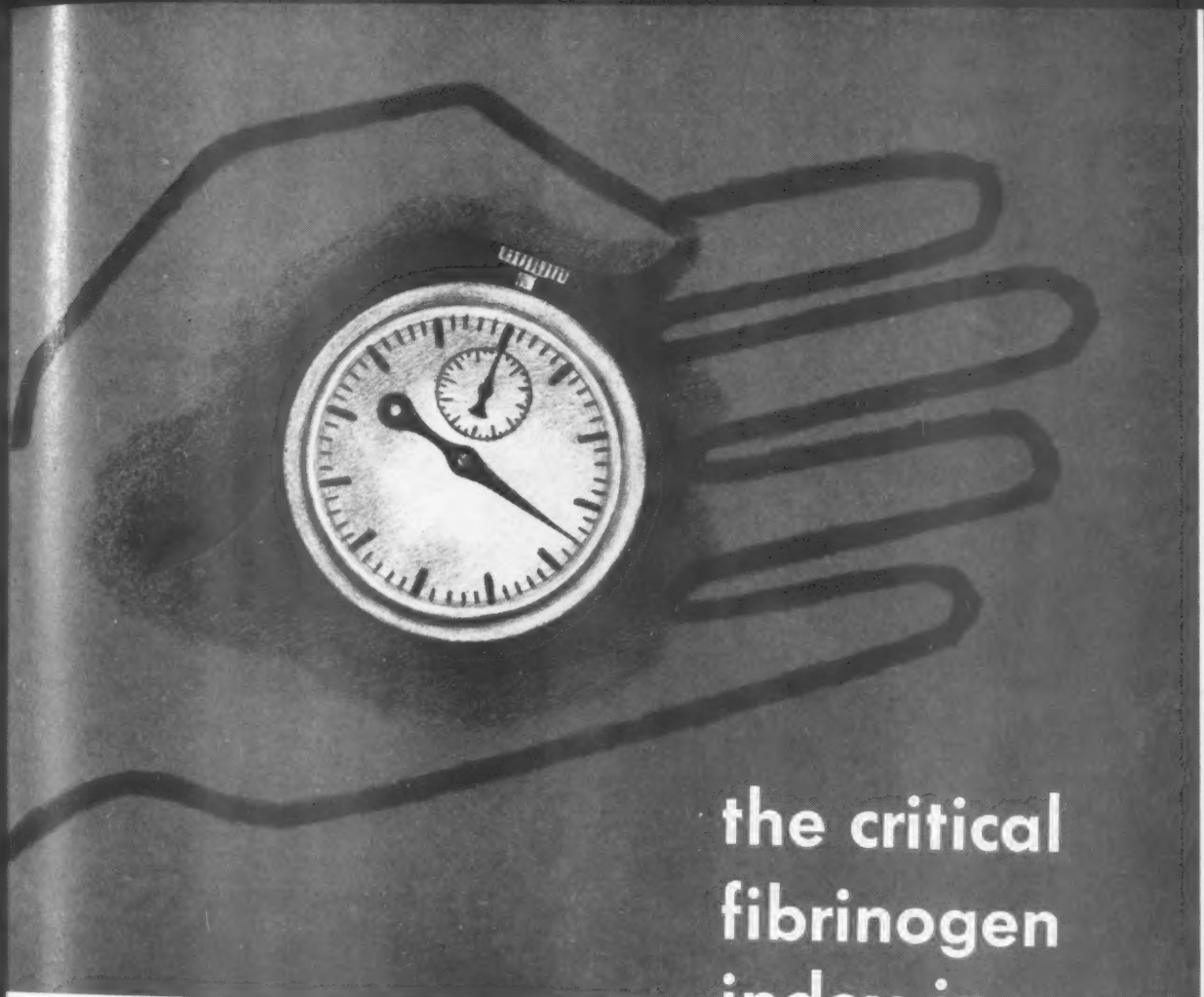
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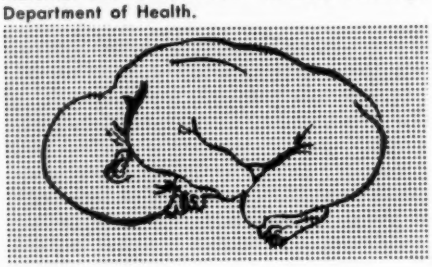
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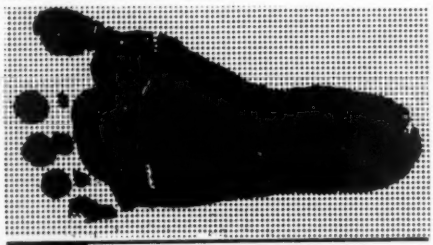
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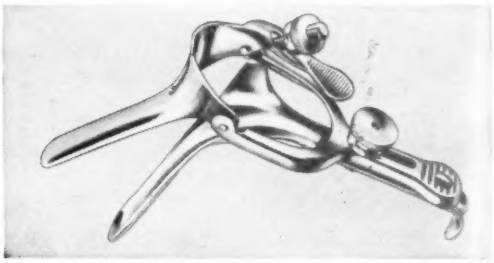
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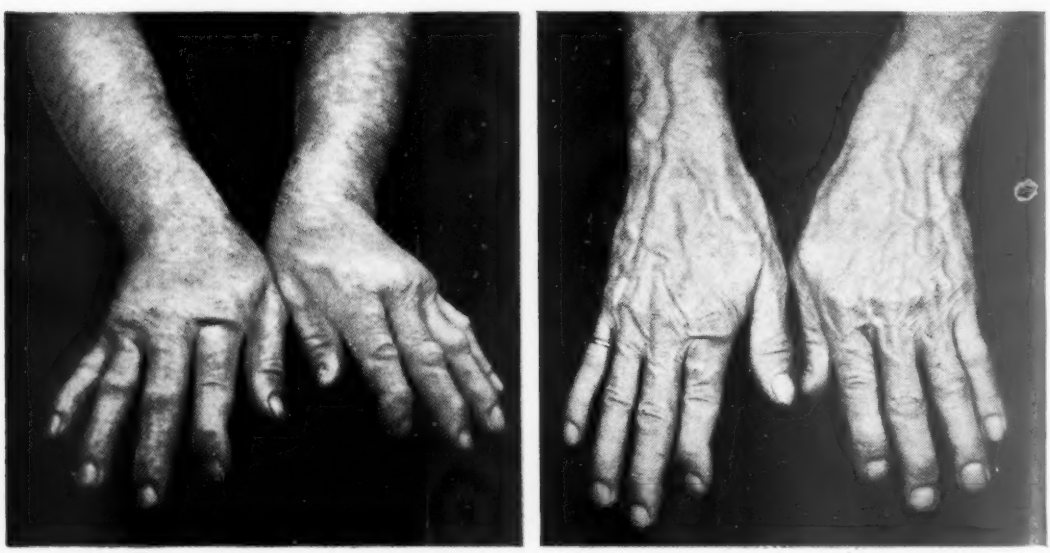
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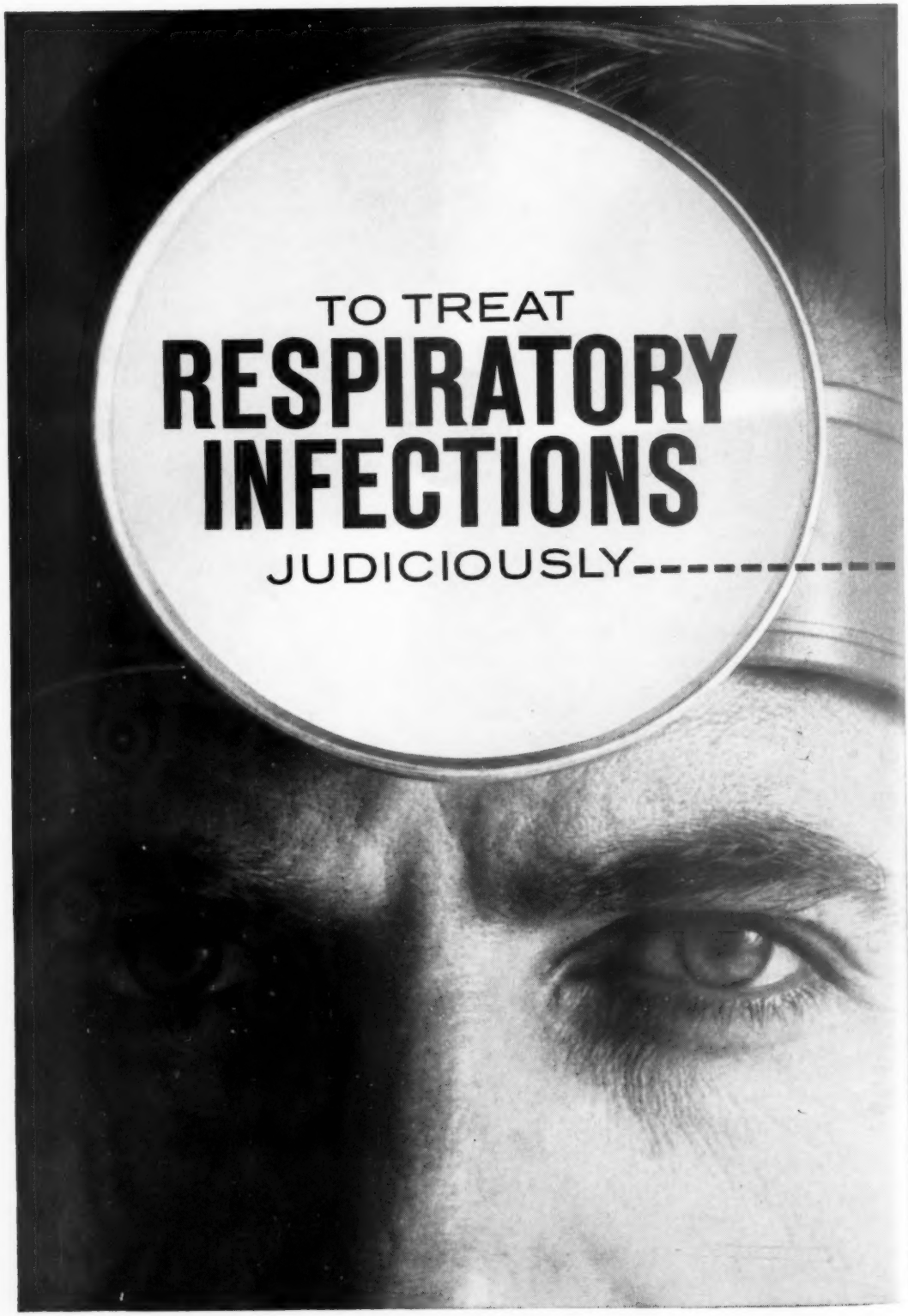
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references: (1) Antos, R. J.: Southwestern Med. *37*:236-237, (April) 1956. (2) Schoenfeld, R. C.: Am. J. Obst. & Gynec. *74*:1114-1115 (Nov.) 1957. (3) Feigen, G. M.: Calif. Med. *86*:41-43 (Jan.) 1957. (4) Towsley, H. A.: J. Michigan M. Soc. *54*:1064-1066, 1138 (Sept.) 1955. (5) Smigel, J. O.; Lowe, K. J.; Hosp, P. H., and Gibson, J. H.: M. Times *86*:1521-1526 (Dec.) 1958.

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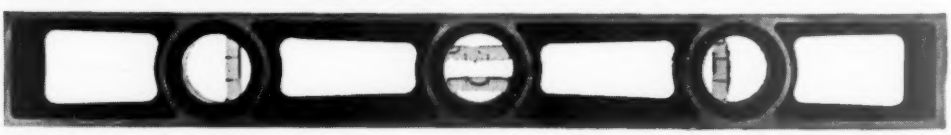
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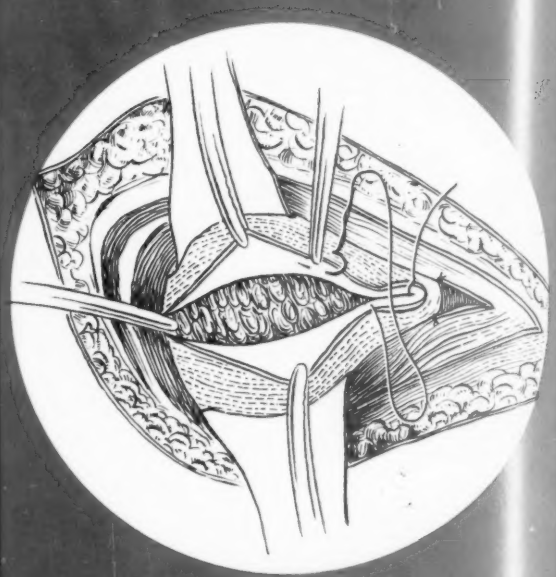
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1. Haden, R.L., et al.: Ann. N.Y. Acad. Sc. 49:641 (May 11) 1948.
2. Cheraskin, E.: J. Am. Dent. Assn. 58:17 (April) 1959.

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References: 1. Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad. Gen. Practice, Sept., 1960.
2. Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am. Soc. Anesth., New York, Oct. 4-7, 1960.

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IN BRIEF

VISTARIL Parenteral Solution is hydroxyzine hydrochloride.
Used preoperatively and postpartum, VISTARIL controls anxiety and fear, helps prevent emesis and smooths recovery. By reducing narcotic requirements substantially, VISTARIL helps to avoid narcotic-induced respiratory depression and hypotension. VISTARIL's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with VISTARIL, and it has a remarkable record of freedom from adverse reactions.

INDICATIONS: In addition to pre- and postpartum and pre- and postoperative tension and emesis, VISTARIL is clinically effective in other anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, certain functional arrhythmias, and pediatric behavior problems.

ADMINISTRATION AND DOSAGE: VISTARIL dosage varies with the state and response of each patient, rather than with weight, and should therefore be individualized by the physician for optimum results. The usual dosage in prepartum and preoperative sedation is 25-50 mg. I.M. or I.V. q. 4 h., p.r.n. Orally, up to 400 mg. per day in divided doses.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

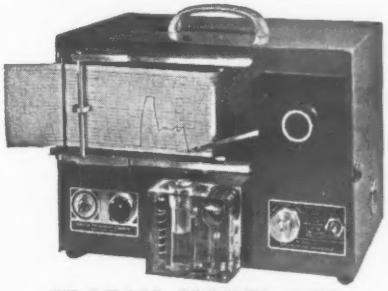
PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgment of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL *Parenteral Solution* (hydroxyzine hydrochloride) – 10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc. VISTARIL *Capsules* (hydroxyzine pamoate) – 25, 50, and 100 mg. VISTARIL *Oral Suspension* (hydroxyzine pamoate) – 25 mg. per 5 cc. teaspoonful.

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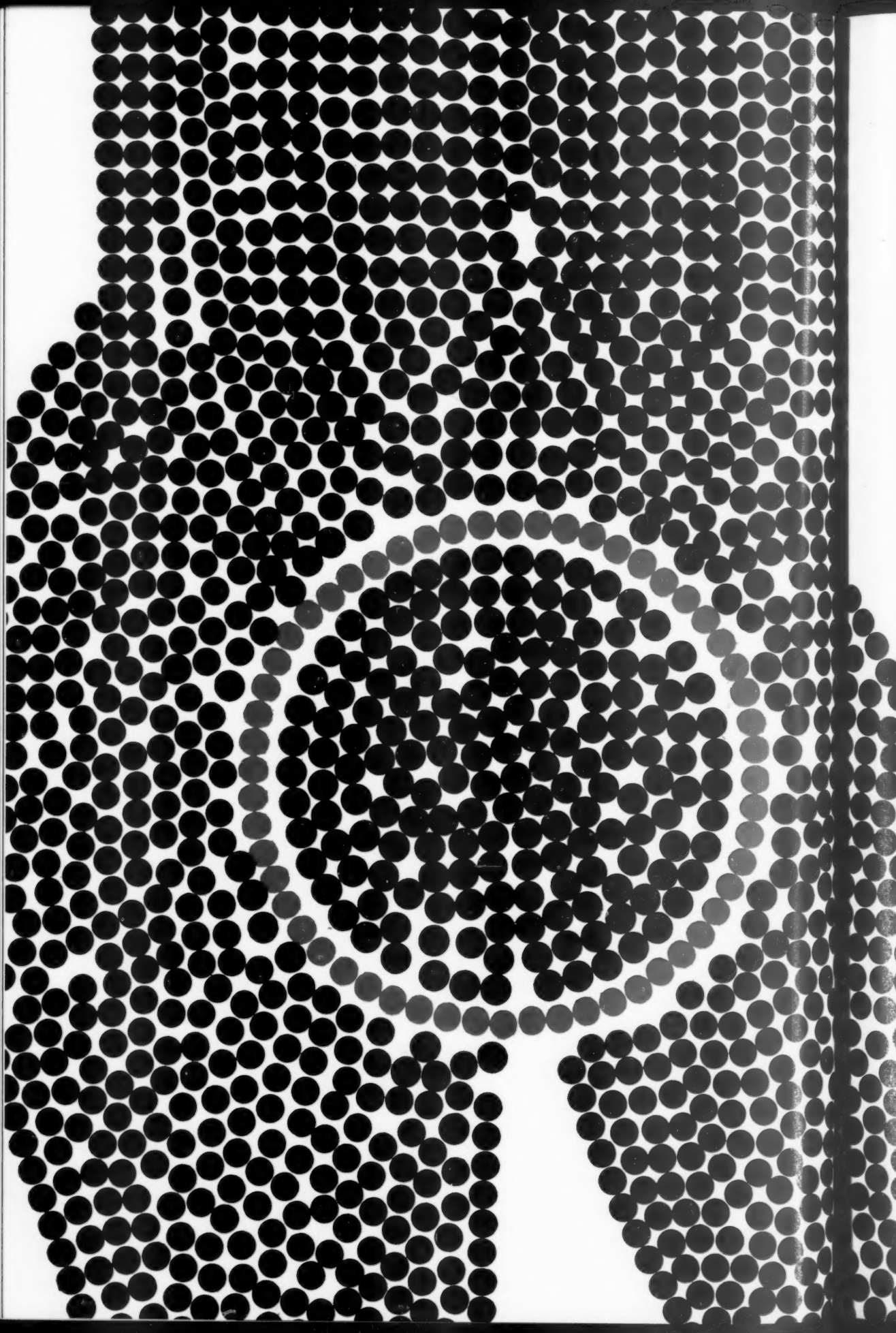


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REFERENCES: 1. N. MULLA AND J. J. McDONOUGH, ANN. NEW YORK ACAD. SC., 82:(ART. 1), 182, 1959. 2. L. E. SAVEL, D. B. GERSHENFELD, J. FINKEL AND P. DRUCKER, IBID., P. 186.

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ERYTHROPOIETIN FOUND TO CONTROL RED CELL FORMATION

A wealth of evidence now confirms the fact that red blood cell production is controlled by the hormone, erythropoietin.[1-3] Demonstrated in human plasma,[4] erythropoietin has shown its activity by producing reticulocytosis[1,5-7] increasing the uptake of Fe^{59} isotope in circulating red cells, and increasing erythrocyte precursors in marrow cultures.[3,8]

erythropoietin levels — new criteria in diagnosis of anemia Since erythropoietin is so rapidly used up in the process of erythropoiesis, increased erythropoietin blood levels can be demonstrated only in severe anemia or for a short time after the start of accelerated production.[9] Thereafter, the effect of the higher levels appears only as an increased erythroid marrow activity.[10] Since the hemopoietic marrow is capable of producing more red cells than normally required, it is postulated that many anemias may be due to inadequate erythropoietin levels—a result of subnormal production or excessive excretion.

how does erythropoietin affect iron metabolism? It is now well established that absorption and utilization of iron is dependent principally upon the degree of bone marrow erythropoiesis.[11,12] The rate of erythropoieses is, in turn, dependent upon erythropoietin levels. Thus, the demand for iron created by accelerated erythropoiesis is satisfied either by increased gastrointestinal absorption of iron or by mobilization of storage iron, or both. Failure to consider inadequate erythropoietin levels would seemingly account for the frequently disappointing results so often seen with the administration of iron alone in the treatment of anemia.

can erythropoietin levels be increased by medication? Cobalt has been shown to be strikingly effective in increasing the production of erythropoietin.[13,14] It is the only known therapeutic agent able to do this. Thus the effect of cobalt-enhanced erythropoietin improves iron utilization and causes a prompt and marked reticulocytosis with subsequent increase in hemoglobin and erythrocytes.

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(1) Gordon, A. S.: Pharmacol. Rev. **39**:1, 1959. (2) Erslev, A. J.: J. Lab. & Clin. Med. **50**:543, 1957. (3) Rosse, W. F., and Gurney, C. W.: J. Lab. & Clin. Med. **53**:446, 1959. (4) Gurney, C. W.; Goldwasser, E., and Pan, C.: J. Lab. & Clin. Med. **50**:534, 1957. (5) Rambach, W. A.; Ait, H. F., and Cooper, J. A. D.: Blood **12**:1101, 1957. (6) Gordon, A. S., **et al.**: Proc. Soc. Exp. Biol. & Med. **92**:598, 1956. (7) Erslev, A. J.: Blood **10**:954, 1955. (8) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood **13**:55, 1958. (9) Stohlman, F., Jr., and Brecher, G.: Proc. Soc. Exp. Biol. & Med. **100**:40, 1959. (10) Kraus, L. M., and Kraus, A. P.: Fed. Proc. **18**:1051, 1959. (11) Bothwell, T. H.; Pirzio-Biroli, G., and Finch, C. A.: J. Lab. & Clin. Med. **51**:24, 1958. (12) Beutler, E., and Buttenwieser, E.: J. Lab. & Clin. Med. **55**:274, 1960. (13) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science **125**:1085, 1957. (14) Murdock, H. R., Jr., and Klotz, L. J.: J. Am. Pharm. A. (Scient. Ed.) **48**:143, 1959.

For a complete background file on erythropoietin, the erythropoietic hormone, please write to the Medical Service Department of:

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1. Crawford, O. B.: Anesthesiology 14:278, 1953. 2. Wiedling, S.: Xylocaine, The Pharmacological Basis For its Clinical Use, Stockholm, Almquist and Wiknell, 1959.

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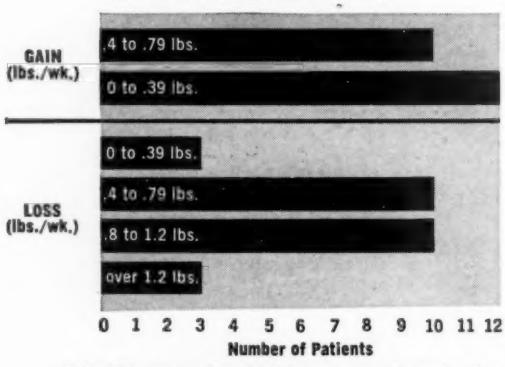
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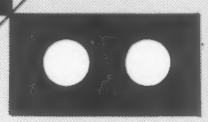
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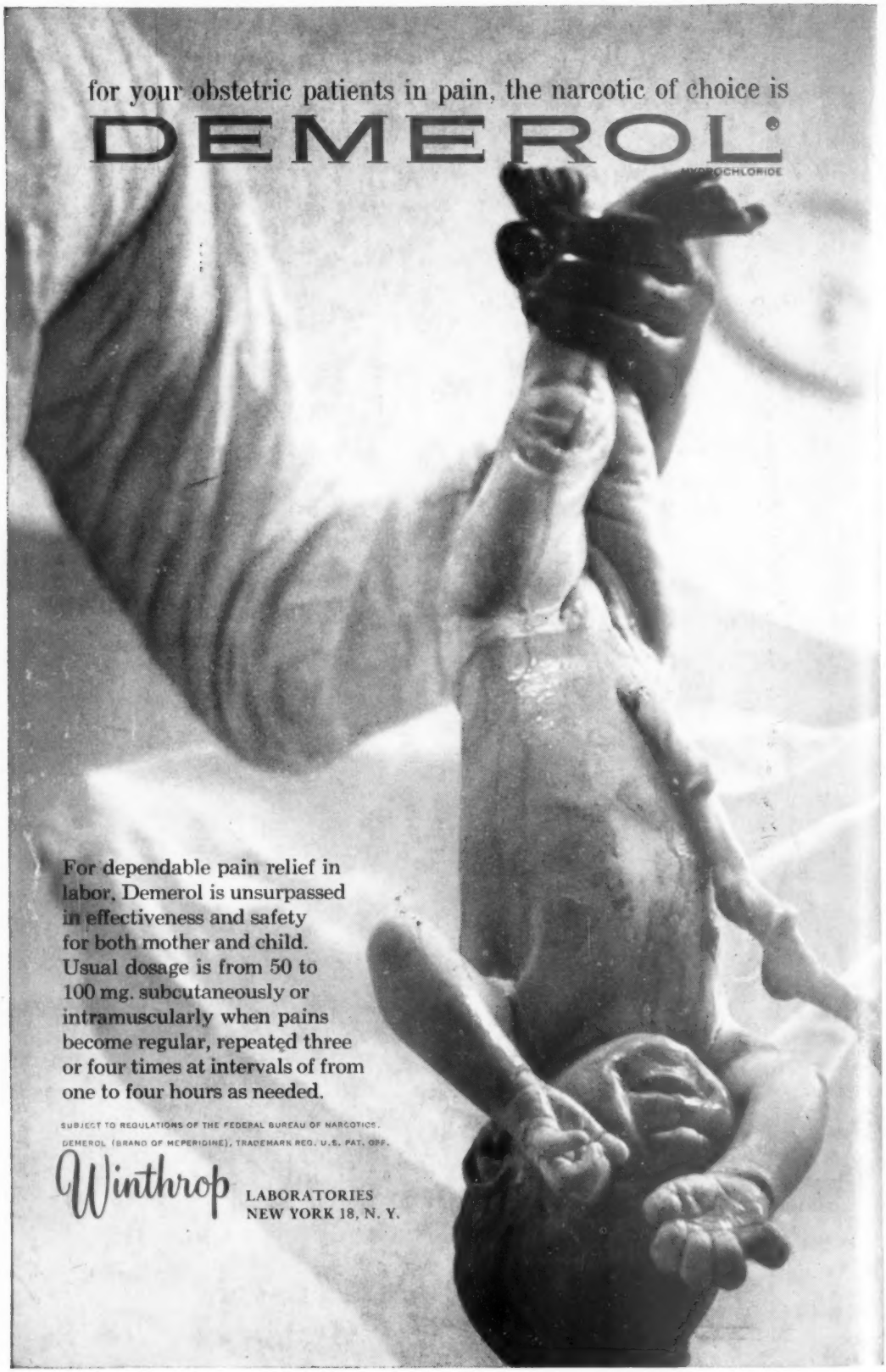
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